Comparative Effectiveness Review
Number 259

Partial Breast Irradiation for Breast Cancer

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers. AHRQ may also seek comments from other Federal agencies when appropriate.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Partial Breast Irradiation for Breast Cancer

Structured Abstract

Objectives. To evaluate the comparative effectiveness and harms of partial breast irradiation (PBI) compared with whole breast irradiation (WBI) for early-stage breast cancer, and how differences in effectiveness and harms may be influenced by patient, tumor, and treatment factors, including treatment modality, target volume, dose, and fractionation. We also evaluated the relative financial toxicity of PBI versus WBI.

Data sources. MEDLINE®, Embase®, Cochrane Central Registrar of Controlled Trials, Cochrane Database of Systematic Reviews, Scopus, and various grey literature sources from database inception to June 30, 2022.

Review methods. We included randomized clinical trials (RCTs) and observational studies that enrolled adult women with early-stage breast cancer who received one of six PBI modalities: multi-catheter interstitial brachytherapy, single-entry catheter brachytherapy (also known as intracavitary brachytherapy), 3-dimensional conformal external beam radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), proton radiation therapy, intraoperative radiotherapy (IORT). Pairs of independent reviewers screened and appraised studies.

Results. Twenty-three original studies with 17,510 patients evaluated the comparative effectiveness of PBI, including 14 RCTs, 6 comparative observational studies, and 3 single-arm observational studies. PBI was not significantly different from WBI in terms of ipsilateral breast recurrence (IBR), overall survival, or cancer-free survival at 5 and 10 years (high strength of evidence [SOE]). Evidence for cosmetic outcomes was insufficient. Results were generally consistent when PBI modalities were compared with WBI, whether compared individually or combined. These PBI approaches included 3DCRT, IMRT, and multi-catheter interstitial brachytherapy. Compared with WBI, 3DCRT showed no difference in IBR, overall survival, or cancer-free survival at 5 and 10 years (moderate to high SOE); IMRT showed no difference in IBR or overall survival at 5 and 10 years (low SOE); multi-catheter interstitial brachytherapy showed no difference in IBR, overall survival, or cancer-free survival at 5 years (low SOE). Compared with WBI, IORT was associated with a higher IBR rate at 5, 10, and over 10 years (high SOE), with no difference in overall survival, cancer-free survival, or mastectomy-free survival (low to high SOE). There were significantly fewer acute adverse events (AEs) with PBI compared with WBI, with no apparent difference in late AEs (moderate SOE). Data about quality of life were limited. Head-to-head comparisons between the different PBI modalities showed insufficient evidence to estimate an effect on main outcomes. There were no significant differences in IBR or other outcomes according to patient, tumor, and treatment characteristics; however, data for subgroups were insufficient to draw conclusions. Eight studies addressed concepts closely related to financial toxicity. Compared with conventionally fractionated WBI, accelerated PBI was associated with lower transportation costs and days away from work. PBI was also associated with less subjective financial difficulty at various time points after radiotherapy.

Conclusions. Clinical trials that compared PBI with WBI demonstrate no significant difference in the risk of IBR. PBI is associated with fewer acute AEs and may be associated with less financial toxicity. The current evidence supports the use of PBI in appropriately selected patients with early-stage breast cancer. Further investigation is needed to evaluate the outcomes of PBI in patients with various clinical and tumor characteristics, and to define optimal radiation treatment dose and technique for PBI.

Contents

Tables

Figure

Appendixes

Executive Summary

Main Points

- There was no significant difference between partial breast irradiation (PBI) and whole breast irradiation (WBI) in terms of ipsilateral breast recurrence (IBR), overall survival, and cancer-free survival at 5 and 10 years (high strength of evidence [SOE]). Evidence for cosmetic outcome was insufficient.
- Individual assessments of various PBI approaches—3-dimensional conformal external beam radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), and multi-catheter interstitial brachytherapy—compared with WBI yielded results consistent with comparing combined PBI approaches with WBI.
- Acute adverse events (AEs) were significantly fewer with PBI compared with WBI, with no apparent difference in late AEs (moderate SOE).
- Compared with WBI, intraoperative radiotherapy (IORT) was associated with a higher IBR rate at 5, 10, and over 10 years (high SOE), with no difference in overall survival (low to high SOE), cancer-free survival (high SOE), or mastectomy-free survival (low to high SOE). There were significantly fewer acute AEs and late AEs Grade ≥2 with IORT.
- Data were insufficient to draw conclusions regarding differences in IBR or other outcomes according to individual patient, tumor, and treatment characteristics.
- Head-to-head comparisons between the different PBI modalities showed insufficient evidence to estimate an effect on main outcomes.
- Compared with conventionally fractionated WBI over several weeks, accelerated PBI was associated with lower transportation costs and days away from work. PBI was also associated with less subjective financial difficulties at various time points after radiotherapy.

Background and Purpose

With an estimated 2.3 million new cases in 2020, breast cancer is the leading cause of global cancer incidence and remains a leading cause of cancer mortality worldwide.[1] Breast conserving therapy has been widely adopted as standard treatment for early-stage breast cancer. Radiotherapy as a component of breast conserving therapy has traditionally included the whole breast volume as a target, now standardly delivered using hypofractionation, with 15-20 treatments delivered over three to four weeks.[2, 3] Although WBI successfully reduces the risk of recurrence after lumpectomy,[4] the protracted course of daily radiotherapy over several weeks represents a significant barrier for many women.[5, 6] Analysis of patterns of recurrence and pathology findings have supported that the area at highest risk for tumor recurrence is adjacent to the lumpectomy cavity.[7, 8] Therefore, PBI has been developed with the hypothesis that limiting the treatment volume may provide similar disease control, enable an accelerated treatment course, and potentially reduce radiation exposure to adjacent normal tissues.[9-12] This hypothesis has been evaluated in clinical trials involving over 15,000 women. However, significant variation in patient selection, treatment technique, and reported clinical outcomes makes interpretation of the data challenging when selecting the preferred treatment for an individual patient.

This systematic review assesses the comparative effectiveness and harms of PBI compared with WBI for early-stage breast cancer, defined as a small tumor less than or equal to 3 cm that

has minimal or no lymph node involvement (N0/1), and how differences in effectiveness and harms are influenced by patient, tumor, and treatment factors, including treatment modality, target volume, dose, and fractionation. We also evaluated the relative financial toxicity of PBI versus WBI.

Methods

We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[13] The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[14] The study protocol was published on the AHRQ website (https://effectivehealthcare.ahrq.gov/products/accelerated-partial-breast-irradiation/protocol) and was registered to the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42021284155). The literature search spanned from each database inception to June 30, 2022.

Results

Twenty-three original studies with 17,510 patients evaluated the comparative effectiveness of PBI, including 14 randomized clinical trials (RCTs), six comparative observational studies, and three single-arm observational studies (Appendix Figure B-1). Eight studies (3 RCTs, 3 comparative observational studies, 1 single-arm observational study, and 1 cost evaluation study) addressed concepts closely related to financial toxicity.

Comparative Effectiveness and Harms of PBI Versus WBI

Thirteen RCTs reported in 38 articles with a total of 15,276 patients were included in the assessment of the comparative effectiveness and harms of PBI versus WBI. The results were generally consistent when PBI approaches were compared with WBI, whether compared individually or combined. These PBI approaches include 3DCRT, IMRT, and multi-catheter interstitial brachytherapy. As a priori, we did not combine IORT with the other PBI modalities and presented the findings separately.

There was no significant difference between PBI and WBI in terms of IBR, overall survival, and cancer-free survival at 5 and 10 years (high SOE). Evidence for the outcome of cosmesis comparing PBI to WBI was insufficient.

3DCRT compared with WBI showed no difference in IBR, overall survival, or cancer-free survival at 5 and 10 years (moderate to high SOE). IMRT compared with WBI showed no difference in IBR and overall survival at 5 and 10 years (low SOE) and better patient-rated cosmesis at 10 years (low SOE). IORT compared with WBI showed a higher IBR rate with IORT at 5, 10, and over 10 years, in contrast to the similar IBR rate observed with other PBI modalities. IORT showed no difference in overall survival, cancer-free survival, or mastectomy-free survival (low to high SOE). There were significantly fewer acute AEs with IORT. Multi-catheter interstitial brachytherapy compared with WBI showed no difference in IBR, overall survival, cancer-free survival at 5 years (low SOE). The rates of acute AEs were significantly less with PBI compared with WBI, with no apparent difference in late AEs (moderate SOE).

Compared with PBI in once-daily fractionation, twice-daily fractionation (3DCRT PBI) was associated with significantly higher rate of patient- and provider-rated adverse cosmetic outcomes and acute AEs. There were no significant differences in IBR or other outcomes

according to patient, tumor, and treatment characteristics; however, data for subgroups were insufficient to draw conclusions.

Comparative Effectiveness and Harms of PBI Modalities

Two RCTs, six comparative observational studies, and three single-arm observational studies with 2,362 patients were included in the assessment of comparative effectiveness and harms of PBI modalities. Head-to-head comparisons between the different PBI modalities showed insufficient SOE to estimate an effect on main outcomes. These comparisons included IMRT versus 3DCRT, multi-catheter interstitial brachytherapy versus 3DCRT, proton versus 3DCRT, single-entry catheter brachytherapy versus 3DCRT, and single-entry catheter brachytherapy versus multi-catheter interstitial brachytherapy.

Financial Toxicity Related to PBI

No studies explicitly addressed the construct of financial toxicity, defined as subjective or objective financial distress and hardship experienced by patients due to cancer-related (or anticipated) treatment; however, eight studies (3 RCTs, 3 comparative observational studies, 1 single-arm observational study, and 1 cost evaluation study) addressed concepts closely related to financial toxicity.

Compared with standard fractionation WBI, accelerated PBI was associated with lower transportation costs and days away from work. PBI was also associated with less subjective financial difficulties at various time points after radiotherapy.

Limitations

The clinical trials included in our aggregate analysis represent a variety of treatment techniques, including several methods of external beam radiotherapy (3DCRT, IMRT, proton therapy), brachytherapy (multi-catheter interstitial brachytherapy, single lumen applicator brachytherapy, multi-lumen applicator brachytherapy), and IORT (low-energy x-ray, electrons). Treatment outcomes of each individual radiation modality were insufficiently reported, which limited the ability to make comparisons across modalities.

Evaluation of outcomes according to patient, tumor, and treatment subgroups was similarly limited by the available data. Many of the included clinical trials did not report subgroup analyses, and often, the subgroups were not able to be combined for aggregate analysis. As a result, we were unable to assess many of the prespecified subgroups. Additionally, the results of subgroup analysis are limited by sample size and the risk of false-positive or false-negative findings. Our results from subgroup analysis may inform future areas of investigation but cannot definitively determine the magnitudes of risk associated with each characteristic. This highlights the need to investigate outcomes of PBI among patients with adverse risk factors.

Radiotherapy technology has developed and dramatically changed over the past two to three decades, with a transition from 2D radiotherapy to routine use of 3D radiotherapy, IMRT, and other advanced planning technologies. These advancements result in improved dose homogeneity that may lower the risk for adverse events. In addition, localization with image guidance improves treatment accuracy, which limits the interpretation of studies that span a wide time interval of significant changes in radiotherapy technology and treatment. Although the volume of the treatment target relative to the breast, dose/fractionation schedule, and planning parameters are recognized as critically important to understand the risks related to treatment,

these data were very limited or unavailable for many studies. Defining an optimal radiation dose, fractionation, and target size using contemporary techniques for treatment planning and image guidance, and characterizing the outcomes of that approach, represent key areas for future study.

Implications and Conclusions

Among patients similar to those enrolled in clinical trials of PBI, there was no significant difference in the risk of IBR compared with WBI. PBI is associated with fewer acute adverse effects, but the risk of IBR among patients treated with PBI who have adverse clinical or pathologic features is unclear. IORT was found to have a significantly higher rate of IBR than was WBI. Further investigation is needed to evaluate outcomes of PBI in moderate risk subgroups with less favorable clinicopathologic features and to define the optimal radiation treatment technique and dose for PBI.

Appropriate patient selection is a critically important aspect of the success of PBI. There is broad consensus in multiple treatment guidelines and systematic reviews that PBI is an acceptable treatment option for patients with clinical and tumor characteristics similar to those represented in clinical trials, for example, postmenopausal age range, estrogen receptor (ER) positive status, grade 1-2, no lymph node involvement, and tumor size ≤ 2 cm. The results presented in this report represent data from 15,276 patients who participated in RCTs of PBI versus WBI, more than three-fold the number of patients who participated in clinical trials that led to the adoption of breast-conserving surgery and WBI as a standard treatment approach.[15] In aggregate, the results of our meta-analysis and systematic review showed no difference between PBI and WBI for selected patients. The finding of reduced acute toxicity with PBI represents a significant finding that will meaningfully inform patient and physician decision making.

Uncertainty remains regarding the magnitude of increased risk associated with features that are perceived as less favorable that were included within the eligibility criteria but represent a minority of patients who participated, for example age <50 years, invasive lobular carcinoma, tumor size 2.1-3 cm, grade 3, ER negative status, Human Epidermal Growth Factor Receptor 2 (HER2) positive status, positive for lymphovascular invasion, or elevated Ki-67. Our analysis revealed the lack of data on the outcomes in these subgroups and highlight the importance of future investigation to develop more robust evidence to inform treatment recommendations.

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1. Introduction

1.1. Background

With an estimated 2.3 million new cases in 2020, breast cancer is the leading cause of global cancer incidence and remains a leading cause of cancer mortality worldwide.[1] Two major developments within the last four decades have resulted in a significant shift in the treatment paradigm for breast cancer. First, screening mammography has resulted in increased detection of smaller tumors, and in countries with widespread adoption of mammography screening, the majority of breast cancer is detected at an early stage.[2] Second, clinical trials have suggested that breast conserving therapy, consisting of breast conserving surgery (i.e., lumpectomy, partial mastectomy) with radiotherapy (or without radiotherapy among select older women[3, 4]), offers equivalent survival to total mastectomy and low rates of recurrence, with the added benefit of breast preservation[5, 6] and other quality-of-life advantages.[7] Hence, breast conserving therapy has been widely adopted as standard treatment for early-stage breast cancer.

Radiotherapy as a component of breast conserving therapy has traditionally included the whole breast volume as a target, now standardly delivered using hypofractionation, with 15-20 treatments delivered over three to four weeks,[8, 9] with increased interest in "ultrahypofractionated" whole breast radiotherapy that is completed in 5-10 fractions.[10] Although whole breast irradiation (WBI) successfully reduces the risk of recurrence after lumpectomy,[11] the protracted course of daily radiotherapy over several weeks represents a significant barrier for many women.[12, 13] Analysis of patterns of recurrence and pathology findings have supported that the area at highest risk for tumor recurrence is adjacent to the lumpectomy cavity.[14, 15] Therefore, partial breast irradiation (PBI) has been developed with the hypothesis that limiting the treatment volume may provide similar disease control, enable an accelerated treatment course, and potentially reduce radiation exposure to adjacent normal tissues.[16-19] This hypothesis has been evaluated in clinical trials involving over 15,000 women, which is more than three times the number of women who participated in the clinical trials that resulted in adoption of breast conserving therapy as a standard treatment several decades ago.[20] Significant variation in patient selection, treatment technique, and reported clinical outcomes makes interpretation of the data challenging when selecting the preferred treatment for an individual patient.

Patient selection is critical to achieve optimal oncologic outcomes for PBI. Notwithstanding the high-quality data from randomized trials of PBI, there is considerable controversy regarding the applicability of PBI for patients who were considered eligible for trial participation but represent a minority of those enrolled. Most women who enrolled in randomized trials of PBI have been postmenopausal, with the median age ranging from 54 to 63 years among the five largest trials of PBI.[21-25] Guidelines from both the American Society for Radiation Oncology (ASTRO)[26] and European Society for Radiotherapy and Oncology (ESTRO)[27] define age ≥50 years as an appropriate selection criterion for PBI. For women aged 40-50 years who are keen to receive PBI but represent a minority of patients who participated in clinical trials, it is challenging to determine whether PBI is associated with similar outcomes to WBI.

Similar observations could be made for a number of tumor features that were included in clinical trials of PBI, such as larger tumor size (2-3 cm), high tumor grade, close margins, Human Epidermal Growth Factor Receptor 2 (HER2) status, and invasive lobular carcinoma. There has not yet been a systematic review to ascertain the role of these factors in determining the suitability for PBI.

The optimal treatment volume, dose, and fractional scheme for PBI remain areas of clinical uncertainty as well. There is considerable heterogeneity in the treatment regimens within reported PBI trials, ranging from 21 Gy in a single fraction to the surface of the lumpectomy cavity for kV based intraoperative radiotherapy (IORT), to 38.5 Gy in 10 fractions given twice daily to a 2 to 2.5 cm expansion on the lumpectomy cavity for external beam PBI. Comparison between the variety of available treatment techniques for PBI have not been systematically evaluated, including several methods of external beam radiotherapy (3-dimensional conformal external beam radiation therapy [3DCRT], intensity-modulated radiation therapy [IMRT], proton therapy), brachytherapy (multi-catheter interstitial brachytherapy, single-entry catheter brachytherapy), and IORT (low-energy x-ray, electrons). This heterogeneity creates a challenge for clinicians in determining the optimal treatment approach, as the total dose, fraction size, treatment delivery schedule, and modality may impact clinical outcomes, including tumor control, cosmesis, toxicity, and quality of life. It is also unclear whether financial toxicity, which is defined as financial distress and hardship related to the cost of treatment and is common among individuals with cancer, is reduced with PBI.[28]

1.2. Purpose and Scope of the Systematic Review

This systematic review assesses the comparative effectiveness and harms of PBI compared with WBI for early-stage breast cancer, defined as a small tumor less than or equal to 3 cm that has minimal or no lymph node involvement (N0/1). The review also addresses how differences in outcomes may be influenced by patient, tumor, and treatment factors, including treatment modality, target volume, dose, and fractionation. The review includes a contextual question about the financial toxicity associated with PBI therapy.

2. Methods

2.1. Review Approach

We developed an analytic framework to guide the process of the systematic review (Figure 1). We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[29] The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[30]

The topic of this report and preliminary Key Questions (KQs) arose through a process involving the public and AHRQ (https://effectivehealthcare.ahrq.gov/about/epc/nomination/). Initially a panel of Key Informants gave input on the KQs to be examined; these KQs were posted on AHRQ's Effective Health Care website for public comment between April 14, 2021, and May 14, 2021, and revised in response to comments. A panel of Technical Experts provided high-level content and methodological expertise throughout development of the review protocol. The final protocol is posted on the Effective Health Care website at https://effectivehealthcare.ahrq.gov/products/accelerated-partial-breast-irradiation/protocol and registered in the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42021284155).

2.2. Key Questions and Contextual Question

2.2.1. Key Questions

KQ 1. In adult women with early-stage breast cancer, what are the comparative effectiveness, adverse events, and cosmetic outcomes of partial breast irradiation compared to whole breast irradiation?

KQ 1a. How does effectiveness of partial breast irradiation (PBI) vary by clinical-pathologic characteristics?

KQ 1b. How do the effectiveness, adverse events, and cosmetic outcomes of partial breast irradiation vary by target volumes, dose-fractionation schemes, motion management, and planning parameters?

KQ 2. In adult women with early-stage breast cancer, what are the comparative effectiveness, adverse events, and cosmetic outcomes of different partial breast irradiation modalities (including multi-catheter interstitial brachytherapy, single-entry catheter brachytherapy, 3-dimensional conformal external beam radiation therapy, intensity modulated radiation therapy, proton radiation therapy, and intraoperative radiotherapy)?

KQ 2a. When there are no eligible comparative studies to address KQ 2 for a particular PBI modality, what are the rates of adverse events in noncomparative series of such modality?

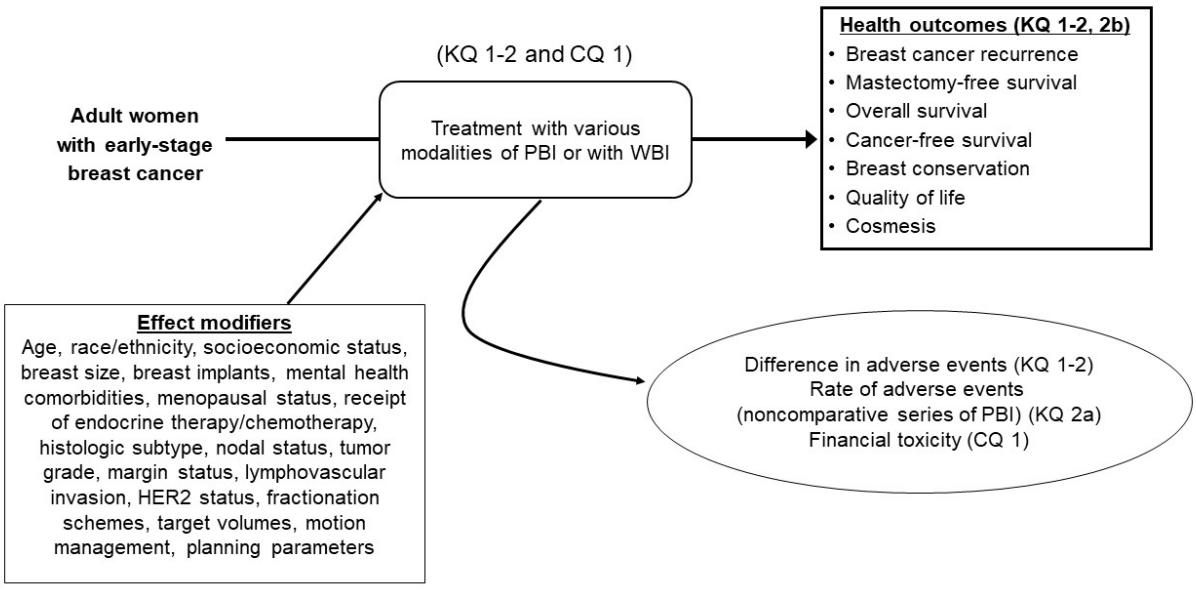
KQ 2b. When there are no eligible comparative studies to address KQ 2 for a particular PBI modality, what are the rates of long-term (>5 years) effectiveness outcomes and cosmesis in noncomparative series of such modality?

2.2.2. Contextual Question (CQ)

CQ1. In adult women with early-stage breast cancer, to what extent does financial toxicity differ between partial and whole breast irradiation?

2.3. Analytic Framework

Figure 1. Analytic framework for Key Questions



Abbreviations: CQ = Contextual Question; HER2 = Human Epidermal Growth Factor Receptor 2; KQ = Key Question; PBI = partial breast irradiation; WBI = whole breast irradiation

2.4. Study Selection

2.4.1. Search Strategy

We searched several bibliographic databases, including Embase® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily, MEDLINE®, Cochrane Central Register of Controlled Trials, Ovid® Cochrane Database of Systematic Reviews, and Scopus® from database inception to June 30, 2022. We also searched Food and Drug Administration, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency, AHRQ Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. We conducted reference mining of existing systematic reviews/meta-analyses, completed trials identified from clinical trial registries, and relevant primary (i.e., randomized clinical trials [RCTs] and observational studies) to identify additional literature. In addition, a Supplemental Evidence and Data for Systematic Reviews (SEADS) portal which collected additional study-specific information from industry stakeholders, professional societies, and researchers from October 18, 2021, to December 9, 2021, was created on the Effective Health Care website and publicized in the Federal Register. The literature search strategy was developed by an experienced medical librarian and peer-reviewed by an independent information specialist. The same medical librarian conducted the literature search. The detailed search strategy is listed in Appendix A.

2.4.2. Inclusion and Exclusion Criteria

The eligible studies for the KQs had to meet all of the following criteria: 1) adult women (18 years and older) with early-stage breast cancer, defined as a small tumor less than or equal to 3 cm that has minimal or no lymph node involvement (N0/1); 2) received one of the six PBI modalities (multi-catheter interstitial brachytherapy, single-entry catheter brachytherapy, 3-dimensional conformal external beam radiation therapy, intensity-modulated radiation therapy, proton radiation therapy, intraoperative radiation therapy [IORT]); 3) compared with whole breast irradiation (WBI) or another PBI modality; 4) reported outcomes of interest (health outcomes and adverse events [AEs]); 5) RCTs and comparative observational studies; for proton radiation therapy, single-arm observational studies with more than 50 patients (as proton radiation therapy was not adequately evaluated in RCTs and comparative observational studies); 6) published in English as peer reviewed full text publication; and 7) publication after the year 2000 (earlier publications are no longer relevant to the current clinical practice). We excluded studies with children (<18 years old), men, and patients with recurrent breast cancer. In vitro studies, studies without original data (e.g., narrative review, editorial, secondary analyses of published trials), single-arm studies with less than 50 patients, and studies published in foreign languages were also excluded. For the CQ, we included all publications that evaluated financial toxicity related to PBI in early-stage breast cancer, regardless of study design and sample size. The detailed inclusion and exclusion criteria for the KQs and CQ are listed in Table 1.

2. Methods

Table 1. PICOTS (population, interventions, comparisons, outcomes, timing, and setting)

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Population	• Adult women (i.e., 18 years and older) with early-stage breast cancer (i.e., a small tumor less than or equal to 3 cm that has minimal or no lymph node involvement (N0/1))	• Animals • Children (i.e., age <18 years) • Men • Recurrent breast cancer
Interventions	For all KQs and CQ1, PBI includes the following modalities: • Multi-catheter interstitial brachytherapy • Single-entry catheter brachytherapy • 3-dimensional conformal external beam radiation therapy • Intensity-modulated radiation therapy • Proton radiation therapy • Intraoperative radiotherapy	• Combination of PBI and WBI
Comparators	KQ 1, CQ 1: WBI KQ 2: A different PBI modality • Multi-catheter interstitial brachytherapy • Single-entry catheter brachytherapy • 3-dimensional conformal external beam radiation therapy • Intensity-modulated radiation therapy • Proton radiation therapy • Intraoperative radiotherapy KQ 2a and 2b: No comparator	None

Outcomes	KQ 1 and 2:
	• Ipsilateral breast cancer recurrence (i.e., tumor bed ipsilateral breast cancer recurrence, elsewhere ipsilateral breast cancer recurrence)
	• Mastectomy-free survival
	• Overall survival
	• Cancer-free survival
	• Contralateral breast cancer recurrence
	• Distant breast cancer recurrence
	• Regional breast cancer recurrence
	• Any breast cancer recurrence
	• Breast conservation
	• Quality of life (e.g., BCTOS, FACT-B, SF-36, Breast Q scale)
	• Patient-reported and physician-assessed cosmesis (e.g., including Harvard Breast Cosmesis Scale/Global Cosmesis Scale, or the EORTC breast cancer cosmetic rating system)
	• Sexual health
	• Adverse events, including scales measuring radiation toxicity:
	  ○ RTOG/EORTC scores
	  ○ LENT-SOMA scales
	  ○ CTCAE scores
	CQ 1: Contextual information about the construct of financial toxicity (i.e., financial distress and hardship)
		None

Timing	At the following intervals: For effectiveness and cosmetic outcomes • ≥1 year to 5 years • >5 years to 10 years • >10 years For adverse events • <3 months • ≥3 months	None
Settings	Any	None

2. Methods

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Study design	KQ 1: • RCTs only KQ 2: • RCTs • Comparative observational studies When there is no eligible study, KQ 2a: • Single-arm observational studies (≥50 patients) KQ 2b: • Single-arm observational studies (≥50 patients and ≥5 year followup) CQ 1: • RCTs • Comparative observational studies • Qualitative studies • Cost-benefit analyses • Surveys All KQs and CQ 1: • Relevant systematic reviews or meta-analyses (used for identifying additional studies)	• In vitro studies • Nonoriginal studies (e.g., narrative reviews, editorials, letters, or erratum), • Cross-sectional (i.e., nonlongitudinal) studies

2. Methods

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Subgroup analysis	KQ 1 and 2: • Age • Treatment schedule (i.e., accelerated, nonaccelerated) • Race/ethnicity • Socioeconomic status • Area Deprivation Index • DCIS vs. invasive disease • Breast size • BMI • Breast implants • Mental health comorbidities • Menopausal status • Receipt of systemic therapy (i.e., none, endocrine therapy, and/or chemotherapy, both) • Histologic subtype (e.g., invasive ductal carcinoma, invasive lobular carcinoma, DCIS, other) • Nodal status (i.e., N0, N1, NX, number of positive nodes) • Nodal assessment (i.e., sentinel lymph node biopsy, axillary lymph node dissection, none) • Tumor grade • Tumor size (i.e., <1 cm, 1-2 cm, 2-3 cm, >3 cm) • Focality (unifocal vs multifocal) • Margin status (i.e., positive, <2 mm, 2-3 mm, >3 mm) • Extensive intraductal component • Ki-67 (<20% vs. ≥ 20%) • ASTRO or ESTRO risk category (i.e., suitable, cautionary, unsuitable; low, intermediate, high) • Germline genetic mutation (e.g., *BRCA1, BRCA2, CHEK2, PALB2, ATM,* etc.) • Cancer-predisposing syndrome • Estrogen receptor status • Progesterone receptor status • Hormone receptor status • Lymphovascular invasion • HER2 status • Prior chemotherapy • Monoelectron therapy • Dermatologic Rheumatologic conditions (i.e., lupus, scleroderma, rheumatoid arthritis) • Dose-fractionation schemes (i.e., accelerated, nonaccelerated, daily vs every other day vs twice daily, total dose, EQD2) • Target volumes (i.e., size of expansion on cavity, diameter of the inflated balloon, size of the planning target volume) • Motion management • Planning parameters (i.e., the diameter of the inflated balloon, the planning target volume, and the dose distribution organ-at-risk constraints and dose received [such as ipsilateral breast V50 and V100], number of beams, PTV coverage goals and constraints) • Number of treatment fields • Image guidance (i.e., MV imaging, kV imaging, cone beam CT, use of clips for localization) • Risk of bias (i.e., low, moderate, high)	None
Publications	• Studies published in English as peer reviewed full text • Published after Year 2000	• Foreign language studies • Conference abstracts

Abbreviations: ASTRO = American Society for Radiation Oncology; BCTOS = Breast Cancer Treatment Outcomes Scale; BMI = body mass index; cm = centimeter; CQ = Contextual Question; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DCIS = ductal carcinoma in situ; EORTC = European Organisation for Research and Treatment of Cancer; EQD2 = Equivalent Dose in 2 Gy fractions; ESTRO = European Society for Radiotherapy and Oncology; FACT-B = Functional Assessment of Cancer Therapy-Breast; HER2 = Human Epidermal Growth Factor Receptor 2; KQ = Key Question; kV = kilovoltage; LENT-SOMA = Late Effects Normal Tissue Task Force- Subjective, Objective, Management, Analytic; mm = millimeter; MV = megavoltage; PBI = partial breast irradiation; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; PTV = planning target volume; RCT = randomized clinical trial; RTOG = Radiation Therapy Oncology Group; SF-36 = Short Form (36) Health Survey; V = volume of a structure receiving a given dose of radiotherapy expressed as either a percentage of the prescription dose (e.g. V100%) or as a quantity of dose (e.g. V30Gy); WBI = whole breast irradiation

Independent reviewers, working in pairs, screened the titles and abstracts of all citations using prespecified inclusion and exclusion criteria. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers, again working in pairs, screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus. When consensus could not be reached, a third reviewer resolved the difference.

2.5. Data Extraction

We developed a standardized data extraction form to extract study characteristics (author, year, study design, inclusion and exclusion criteria, patient characteristics, intervention, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form was tested by all study team members using randomly selected studies. Reviewers worked independently to extract study details. A second reviewer reviewed data extraction and resolved conflicts. When the included studies did not report all necessary information (e.g. methods and results), we contacted authors directly. DistillerSR® was used to create data extraction forms and facilitate data extraction.

2.6. Risk of Bias Assessment

For KQs, we evaluated the risk of bias of the included RCTs using the Cochrane Collaboration's Risk of Bias 2 tool[31] to assess bias from the randomization process, deviation from intended interventions, missing outcome data, outcome measurement, selective reporting, and other sources. For comparative and single-arm observational studies, we selected appropriate items from the Newcastle-Ottawa Scale.[32] For studies reporting on CQ 1 on financial toxicity, we did not evaluate risk of bias since this contextual information was narratively summarized. One reviewer independently rated risk of bias for all studies. A second reviewer reviewed the ratings and resolved conflicts.

2.7. Data Synthesis and Analyses

We qualitatively summarized key features/characteristics (e.g. study populations, design, intervention, outcomes, and conclusions) of the included studies and present the findings in evidence tables for each KQ.

Table 2 lists the definition of outcomes used in the report.

Table 3 lists the categories of AEs and examples. We differentiated acute and late AEs using the original authors' definition. In most cases, AEs less than 3 months after radiotherapy were defined as acute AEs; while AEs more than 3 months were defined as late AEs.

2. Methods

Table 2. Definition of health outcomes

Outcome	Definition
Ipsilateral breast recurrence (IBR)	Recurrence of histologically confirmed invasive or in situ breast cancer in the ipsilateral breast. This is often reported as "ipsilateral breast tumor recurrence" in the published data and is described in our report as "ipsilateral breast recurrence" to be consistent with the STEEP 2.0 definition[24, 33].
Cancer-free survival	Absence of local, regional, or distant recurrence of breast cancer, or death from breast cancer
Overall survival	Patients who remain alive (death due to any cause)
Cosmesis	Proportion of patients with fair or poor cosmetic score using the Harvard Breast Cosmesis Scale or the European Organisation for Research and Treatment of Cancer Breast Cancer Cosmetic Rating System
Distant breast cancer recurrence	Recurrence of breast cancer in distant sites
Contralateral breast cancer recurrence	Recurrence of breast cancer in the opposite breast that did not receive radiotherapy
Tumor bed IBR	Breast cancer recurrence within the ipsilateral breast in close proximity to the tumor bed (within 2 cm or in the same quadrant)
Elsewhere IBR	Breast cancer recurrence within the ipsilateral breast away from the tumor bed (in a different quadrant or >2 cm from tumor bed)

Abbreviations: cm = centimeter; IBR = ipsilateral breast recurrence; STEEP 2.0 = Standardized Definitions for Efficacy End Points version 2.0

Table 3. Categories of adverse events

Type of Adverse Event	Example
Skin	Erythema, patchy atrophy, pigmentation, skin color change, radiation dermatitis
Telangiectasias	Telangiectasias
Extremity	Arm lymphedema, difficulty raising arm, arm or shoulder pain
Wound	Bleeding, infection, hematoma, seroma
Breast edema	Breast edema, breast swelling
Breast induration or fibrosis	Breast induration, fibrosis
Pain	Breast oversensitive, chronic pain
Soft tissue breast	Breast parenchyma, fat necrosis
General	Fatigue
Pulmonary	Pneumonitis
Rib fracture	Rib fracture
Cardiac	Ischemic heart disease

We conducted meta-analysis, whenever appropriate (i.e., 2 or more studies) address the same PICOTS (population, interventions, comparisons, outcomes, timing, and setting) and provide point estimates and dispersion measures) to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. As a priori, we did not combine IORT with the other PBI modalities, because it is distinctly different from other PBI modalities. Radiotherapy in PBI and WBI is delivered by defining a target volume and calculating the dose it receives, whereas IORT is an exception to this standard approach in which the dose received by a defined target is not evaluated.[34] We also did not meta-analyze quality of life and did not combine comparative observational studies with RCTs. Last, studies addressing CQ 1 and single-arm studies were described and summarized narratively.

Analyses were based on the "intention-to-treat" principle for RCTs or number of patients initially receiving the interventions at the start of observational studies. For studies with multiple publications, when there was discrepancy between the publications, we prioritized data from later publications with more complete and longer followup. Relative risk (RR) and corresponding 95 percent confidence intervals (CIs) were extracted or calculated for binary outcomes. We dichotomized cosmesis scales to poor/fair versus good/excellent. Since one patient may suffer multiple adverse events, we calculated the incidence rate ratio for this

outcome, which is defined as the ratio of the incidence rate of events within a given time between the intervention and the comparison groups. As suggested by empirical work,[35] data from noninferiority trials were combined with those from trials that did not apply a noninferiority margin. Meta-analyses were conducted based on length of followup: for health outcomes: ≥1 year to 5 years, >5 years to 10 years, >10 years; for adverse events: ≤3 months (acute AE), >3 month (late AE). We used the DerSimonian-Laird random effect model with Hartung-Knapp-Sidik-Jonkman variance correction to combine direct comparisons between treatments.[36] We evaluated heterogeneity between studies using the I^2 indicator, which measures percentage of variations in effect sizes reported by the studies due to heterogeneity. To further explore heterogeneity, we conducted prespecified subgroup analyses based on age, lymphovascular invasion, adjuvant therapy, accelerated partial breast irradiation suitability, disease stage (ductal carcinoma in situ vs. invasive disease), estrogen receptor (ER) status, Human Epidermal Growth Factor Receptor 2 (HER2) status, histology , hormone receptor status, tumor size, tumor grade, Ki-67 proliferative index, lymph node status, menopausal status, molecular subtype, molecular subtype, progesterone receptor (PR) status, resection margins, planning parameters (IORT immediately after lumpectomy vs. delayed IORT), dose-fractionation schemes (accelerated vs. nonaccelerated), treatment dose (twice per day, once per day, and once every 2 days) and risk of bias (low, moderate, and high risk of bias). We were unable to conduct other prespecified subgroup analyses (e.g. race/ethnicity, socioeconomic status, breast size) as the studies did not provide specific data for these factors. We evaluated the robustness of the findings (i.e., sensitivity analysis) comparing analyses that produced RR as an outcome measure, to hazard ratio estimates reported by the studies, and combining studies at the longest followup. One study[37] reported results from a RCT conducted between 1986 and 1990 with antiquated radiation techniques that are no longer relevant to current practice but, otherwise, met our inclusion criteria. We included this study as a sensitivity analysis. We were unable to evaluate potential publication bias due to the small number of studies included in a meta-analysis (n<10). All statistical analyses were conducted using Stata version 17.0 (StataCorp LLC, College Station, TX, USA).

2.8. Grading the Strength of Evidence for Major Comparisons and Outcomes

We graded the strength of evidence (SOE) for KQs following the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[29] We graded SOE for the critical effectiveness outcomes: ipsilateral breast recurrence, mastectomy-free survival, cancer-free survival, overall survival, and cosmesis. We graded SOE for overall acute and late AEs comparing WBI to combined PBI modalities. These outcomes were chosen because they are either clinically important from a patient's perspective or highly relevant for stakeholders' decision making.

SOE derived from RCTs started with a rating of high and SOE derived from observational studies started as low.[29] SOE was rated down due to methodological limitations of the studies (i.e. risk of bias); imprecision (based on the size of the body of evidence, number of events, and confidence intervals); indirectness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs. surrogates); inconsistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); or increased likelihood of reporting and publication bias.

We lowered SOE rating for the risk of bias when all the studies in a particular comparison had high or unclear risk of bias. If estimates from high and low risk of bias studies were available and similar, we combined them and did not rate down SOE. If estimates were different, we only used the low risk of bias estimate and did not rate down SOE (although this could lead to imprecise estimates).

We considered estimates to be precise if the CI of RR did not overlap benefit and harms and the sample size was 1,000 or more. We also considered an effect to be precise if the CI of RR did not overlap the benefit and harms and the risk difference CI was within 30 per 1,000.[38, 39] We rated down one level if the effect was statistically significant but the sample size <1,000, the effect was insignificant but sample size >2,000, or the effect was insignificant but the risk difference CI exceeded 30 per 1,000. We rated down by two levels if the effect was insignificant and the sample size was 400-1,999. We rated down by 3 levels if the effect was insignificant and the sample size was <400. We also considered whether outcome designation (mortality vs. survival) affected imprecision judgments.

We rated down for inconsistency when I^2 exceeded an arbitrary cutoff >60 percent and visual inspection of forest plots suggested substantial variability in point estimates.

Based on this assessment and the initial study design, we assigned SOE rating as high, moderate, low, or 'insufficient evidence to estimate an effect' (Table 4).

Table 4. Definition of strength of evidence ratings

SOE rating	Definition
High	We are very confident that the estimate of effect lies close to the true effect (the body of evidence has few or no deficiencies and is judged to be stable)
Moderate	We are moderately confident that the estimate of effect lies close to the true effect (the body of evidence has some deficiencies and is judged to be likely stable).
Low	We have limited confidence that the estimate of effect lies close to the true effect (the body of evidence has major or numerous deficiencies and is likely unstable).
Insufficient	We have no evidence, are unable to estimate an effect, or have no confidence in the estimate of effect.

Abbreviations: SOE = strength of evidence

We produced summary of evidence tables that provided for each comparison and for each outcome: data source, effect size, SOE rating; and rationale for judgments made on each domain of evidence rating.

2.9. Assessing Applicability

We followed the procedures outlined in the AHRQ Methods Guide to assess the applicability of the findings within and across studies.[29] Applicability for each outcome was summarized and presented qualitatively using the PICOTS framework and not a specific checklist or scale. The following factors that may affect applicability have been identified, including patient factors (e.g. age, menopausal status, race, ethnicity, socioeconomic status), tumor characteristics (e.g. nodal status, tumor size/grade, histology), intervention factors (e.g. dose-fractionation schemes, target volumes, planning parameters, number of treatment fields), comparisons (e.g. type of comparators), outcomes (e.g. use of unvalidated or nonstandardized outcomes), settings, and study design features (e.g. observational studies, RCTs). We used this information to evaluate the applicability of the evidence to real-world clinical practice in typical U.S. settings. We reported any limitations in applicability of individual studies in the evidence tables and limitations of applicability of the whole body of evidence in the summary of evidence tables.

2.10. Peer Review and Public Commentary

Experts in the fields of radiation oncology and breast surgical oncology as well as other stakeholders provided external peer review of this draft report; AHRQ also provided a review of the draft report. The draft report was then posted on the AHRQ Effective Health Care website for public comment from July 1 to July 29, 2022.

3. Results

3.1. Literature Searches and Evidence Base

For Key Question (KQ) 1 and KQ 2, our literature search identified 6,727 citations. There were 23 original studies reported in 52 articles with a total of 17,510 patients who met inclusion criteria (Appendix B.). Of the 23 studies, there were 14 randomized clinical trials (RCTs)[21-25, 37, 40-72] six comparative observational studies[73-81] and three single-arm observational studies.[82-85] eight studies were conducted in the United States,[72, 74, 79-85] nine in Europe,[24, 25, 37, 40, 54, 58-70, 73, 75-78] two in Asia,[51, 71] and four in multiple countries.[21-23, 41-50, 52, 53, 55-57] Range of median followup was from 1 to 17 years. Thirteen studies were included in KQ 1,[21-25, 37, 40-71] and 11 in KQ 2.[66-70, 72-85]

The included studies evaluated intensity-modulated radiation therapy (IMRT) (3 RCTs,[24, 40, 58-61, 72] 1 comparative observational study[73]), proton (1 comparative observational study,[79] 3 single-arm observational studies[82-85]), intraoperative radiotherapy (IORT) (2 RCTs,[41-50, 62, 63] 1 comparative observational study[75-78]), 3-dimensional conformal external beam radiation therapy (3DCRT) (4 RCTs,[25, 51, 54, 64-70] 4 comparative observational studies[73, 74, 79, 80]), single-entry catheter brachytherapy (three comparative observational studies[74, 80, 81]), multi-catheter interstitial brachytherapy (one RCT,[23, 55-57] two comparative observational studies[80, 81]), and multiple modalities (four RCTs,[21, 22, 37, 52, 53, 66-70] one comparative observational study[75-78]). A list of the studies excluded at the full-text review stage is in Appendix C, and the characteristics of included studies are included in Appendix Tables D.1 and D.2. A search of clinical trial registries identified 46 ongoing clinical trials.

For Contextual Question (CQ) 1 (financial toxicity), we did not identify studies that explicitly addressed the construct of financial toxicity, defined as subjective or objective financial distress and hardship experienced by patients due to cancer-related (or anticipated) treatment. However, we identified eight studies[55, 58, 75, 82, 86-89] that addressed various closely related concepts, such as direct nonhealthcare costs (e.g., transportation to receive care) and indirect costs (e.g., loss of productivity). These eight studies include three RCTs,[55, 58, 87] three comparative observational studies,[75, 86, 88] one single-arm observational study,[82] and one cost evaluation study.[89] Two studies were conducted in the United States, five in Europe, and one in India. The partial breast irradiation (PBI) modalities evaluated were IORT (n=2), multi-catheter interstitial brachytherapy (n=3), IMRT (n=2), 3DCRT (n=2), single-entry catheter brachytherapy (n=1), and proton radiation therapy (n=1). Four studies evaluated time away from work, transportation to receive care, and related costs in monetary value.

3.2. Key Question 1

3.2.1. KQ 1 Key Points

- At 5 and 10 years of followup, there was no significant difference between PBI and whole breast irradiation (WBI) in terms of ipsilateral breast recurrence (IBR) overall survival, and cancer-free survival (high strength of evidence [SOE]).
- Evidence for cosmetic outcomes were insufficient.
- When various PBI approaches (3DCRT, IMRT, and multi-catheter interstitial brachytherapy) were compared individually to WBI, the results were generally consistent with when these PBI approaches were combined and compared with WBI.

- 3DCRT compared with WBI showed no difference in IBR, overall survival, or cancer-free survival at 5 and 10 years (moderate to high SOE).
- IMRT compared with WBI showed no difference in IBR or overall survival at 5 and 10 years (low SOE) and better patient-rated cosmesis at 10 years (low SOE).
- Multi-catheter interstitial brachytherapy compared with WBI showed no difference in IBR, overall survival, and cancer-free survival at 5 years (low SOE).
- Compared with WBI, there were significantly fewer acute adverse events (AEs) with PBI with no apparent difference in late AEs (moderate SOE).
- The data were insufficient to draw conclusions regarding differences in IBR or other outcomes according to individual patient, tumor, and treatment characteristics.
- Compared with once-daily fractionation, PBI with twice-daily fractionation was associated with significantly higher rates of patient- and provider-rated adverse cosmetic outcomes and acute AEs.
- Compared with WBI, IORT was associated with a higher IBR rate at 5, 10, and over 10 years (high SOE). IORT showed no difference in overall survival (low to high SOE), cancer-free survival (high SOE), or mastectomy-free survival (low to high SOE). There were significantly fewer acute AEs and late AEs grade ≥2 with IORT.

3.2.2. KQ 1 Results

Thirteen RCTs reported in 38 articles were included in KQ 1 with a total of 15,276 patients (Appendix B).[21-25, 37, 40-71] Average age of the patients were 58.83 years (range: 25-84) with average tumor size of 1.31 cm; 74.61 percent with tumor grade 1 or 2; 6.77 percent with lobular cancer; 89.48 percent with no lymph node involvement; and 91.76 percent with positive estrogen receptor (ER). Seven studies were conducted in Europe,[24, 25, 37, 40, 54, 58-70] two in Asia,[51, 71] and four in multiple countries.[21-23, 41-50, 52, 53, 55-57] The range of median followup was from 2.2 to 17 years.

These studies evaluated IMRT (2 RCTs[24, 40, 58-61]), IORT, (2 RCTs,[41-50, 62, 63]), 3DCRT (6 RCTs[22, 25, 51-54, 64-71]), multi-catheter interstitial brachytherapy (1 RCT[23, 55-57]), multiple modalities (3 RCTs[21, 37, 66-70]), and WBI (13 RCTs,[21-25, 37, 40-71]). The characteristics of included studies are included in Appendix Table D.1. Effectiveness, AEs, and cosmetic outcomes are summarized in Tables 5, 6, 7, and 8. Sensitivity analyses showed no significant difference from the main findings (Appendix Table L.1-L.3).

3.2.2.1. PBI Versus WBI

3.2.2.1.1. Ipsilateral Breast Tumor Recurrence

IBR was not statistically significantly different with PBI at 5 years (relative risk [RR]: 1.34; 95% confidence interval [CI]: 0.83 to 2.18; I^2= 0%; high SOE) or at 10 years (RR: 1.29; 95% CI: 0.87 to 1.91; I^2= 0%; high SOE). The relative risk for IBR with results reported at >10-year followup is similar to that reported at 5- and 10-year followup; however, these findings are limited by having only two studies reporting >10-year followup.[65, 68]

3.2.2. Results, Key Question 1: KQ 1 Results

3.2.2.1.2. Overall Survival

Compared with WBI, PBI was associated with no significant difference in overall survival at 5 years (RR: 1.00; 95% CI: 0.99 to 1.01; I^2= 0%; high SOE) and 10 years (RR: 1.01 95% CI: 0.97 to 1.04; I^2= 29%; high SOE). The evidence is insufficient at >10 years.

3.2.2.1.3. Cancer-Free Survival

Compared with PBI, cancer-free survival associated with WBI was not significantly different at 5 years and 10 years with nearly identical results in both arms (5-year RR: 1.00; 95% CI: 0.98 to 1.02, I^2= 0%, high SOE; 10-year RR: 0.97, 95% CI: 0.92 to 1.02, I^2= 0%, high SOE). The evidence is insufficient at >10 years.

3.2.2.1.4. Cosmesis

There was no significant difference in patient and provider reported cosmetic outcomes at 5 years and 10 years (insufficient SOE [22-24, 40, 51-53, 55-61, 64-70]). The Budapest trial reported that PBI was associated with significantly better provider-rated cosmesis at >10 years [66-70]; the Florence trial[24, 58-61] reported significantly better patient-rated cosmesis with PBI at 10 years; and the IMPORT LOW study reported significantly lower rates of breast appearance change with PBI.[54] The GEC-ESTRO study reported no significant difference in cosmetic results for multi-catheter interstitial brachytherapy compared to WBI.[56] The RAPID trial[22, 52, 53], in which PBI was delivered in twice daily treatment for 10 fractions with external beam radiotherapy, found significantly worse patient-rated and provider-rated cosmesis with PBI at 5 and 10 years.

3.2.2.1.5. Adverse Events

PBI was associated with significantly fewer acute AEs (incidence rate ratio [IRR]: 0.53; 95% CI: 0.31 to 0.92; I^2= 88%) and AEs grade 2 and above (IRR: 0.21; 95% CI: 0.07 to 0.62; I^2= 94%), compared with WBI.

Total number of late AEs (IRR: 0.85; 95% CI: 0.44 to 1.62; I^2= 97%) and late AEs grade ≥2 (IRR: 0.75; 95% CI: 0.28 to 2.03; I^2= 96%) were not statistically different for WBI compared with PBI, with considerable heterogeneity (I^2>90%) across the studies.

3.2.2.1.6. Other Outcomes

PBI and WBI were not statistically different in the risk of tumor bed IBR at 5 years and 10 years, with similar findings from a solitary study with >10-year followup. Analogous to the findings for tumor bed IBR, WBI was not significantly different to PBI in reducing the risk of elsewhere IBR at 5 years and 10 years. Only one study (Budapest trial) reported the rate of elsewhere IBR at >10 years, which was not statistically significantly different between PBI versus WBI.[66-70] Compared with PBI, contralateral breast cancer was not increased with WBI at 5 years, 10 years, and >10 years. WBI was not significantly different to PBI for distant breast cancer recurrence or overall survival at 5, 10, and >10 years.

Three studies evaluated quality of life. The Florence trial[58] reported that, compared with WBI, IMRT PBI was associated with significantly better quality of life (global health status, functional and symptom) measured by European Organization for Research and Treatment of Cancer quality of life questionnaire-C30 (EORTC QLQ-C30) scales and symptom scales (breast and arm symptoms) measured by European Organization for Research and Treatment of Cancer quality of life questionnaire-BR 23 (EORTC QLQ-BR23) at 2 years. The GEC-ESTRO trial[55] found that multi-catheter interstitial brachytherapy was associated with better breast symptoms

and arm symptoms after PBI compared with WBI at 3-month followup, and 5-year followup (measured by EORTC QLQ-BR23). There was no significant difference on global health status at 5 years (measured by EORTC QLQ-C30). A third RCT[71] compared 3DCRT PBI to WBI and found no significant difference between the two groups in any subscales measured by EORTC QLQ-C30 and EORTC QLQ-BR23 at one year.

3.2.2.2. IORT Versus WBI

3.2.2.2.1. Ipsilateral Breast Tumor Recurrence

IORT was associated with a significantly higher rate of IBR than WBI at 5 years (RR: 3.92; 95% CI: 2.44 to 6.32; I^2=74%, high SOE) and 10 years (RR: 7.61; 95% CI: 3.48 to 16.60; I^2= not applicable [N/A]; high SOE). One study[62, 63] with long-term followup reported significantly higher IBR with IORT compared with WBI at 10 years (RR: 7.61; 95% CI: 3.48 to 16.60; I^2= N/A; moderate SOE) and >10 years (RR: 4.40; 95% CI: 2.58 to 7.48; I^2= N/A, high SOE).

3.2.2.2.2. Overall Survival

When IORT was compared with WBI, there was no significant difference in overall survival at 5 years (RR: 1.00; 95% CI: 0.93 to 1.08; I^2= 0%; high SOE), 10 years (RR: 0.98; 95% CI: 0.95 to 1.01; I^2= N/A; low SOE), and >10 years (RR: 1.01; 95% CI: 0.88 to 1.15; I^2= 0%; high SOE).

3.2.2.2.3. Cancer-Free Survival

Cancer-free survival associated with WBI was not significantly different to that observed with IORT at 5 years (RR: 1.00; 95% CI: 0.97 to 1.02; I^2= N/A; high SOE).

3.2.2.2.4. Mastectomy-Free Survival

There was no significant difference in mastectomy-free survival between WBI and IORT at 5 years (RR: 0.97; 95% CI: 0.95 to 1.00; I^2=N/A; high SOE), 10 years (RR: 0.99; 95% CI: 0.94 to 1.03; I^2=N/A; low SOE), and >10 years (RR: 0.99; 95% CI: 0.97 to 1.02; I^2= N/A; high SOE).

3.2.2.2.5. Adverse Events

IORT was associated with significantly fewer acute AEs (IRR: 0.16; 95% CI: 0.06 to 0.40; I^2= N/A) and late AE grade 2 and over (IRR: 0.26; 95% CI: 0.11 to 0.64; I^2= N/A), when compared with WBI. There was no significant difference in total number of late AEs.

3.2.2.2.6. Other Outcomes

The ELIOT trial reported IORT was associated with significantly more tumor bed IBR at 5 years and elsewhere IBR at 5 years.[62, 63] There was no significant difference in contralateral breast cancer recurrence and distant breast cancer recurrence at 5 years, 10 years, and >10 years, when compared with WBI.

3.2.2.3. 3DCRT PBI Versus WBI

There was no significant difference between 3DCRT PBI and WBI in IBR, overall survival, or cancer-free survival at 5 years, 10 years, and >10 years (moderate to high SOE for 5- and 10-year results; insufficient SOE for >10-year results). There was insufficient evidence in provider reported cosmesis at 5 years. In one clinical trial of 3DCRT PBI delivered in twice-daily

fractions compared to WBI, 3DCRT PBI was associated with a significantly higher rate of provider-reported fair or poor cosmetic outcome (RR: 2.14; 95% CI:1.74 to 2.61; I^2=N/A; moderate SOE) and patient-reported fair or poor cosmetic outcome (RR: 2.32; 95% CI: 1.84 to 2.91; I^2=N/A; moderate SOE) compared with WBI at 10 years.[22, 52, 53] There were no significant differences in elsewhere IBR at 5 years; significantly higher elsewhere IBR was observed for 3DCRT PBI, compared with WBI, at 10 years. There were no differences between 3DCRT PBI and WBI in contralateral breast cancer, distant breast cancer recurrence, and tumor bed IBR at 5 years and 10 years, acute AEs and late AEs. An RCT[71] found no significant difference between 3DCRT and WBI in any subscales measured by EORTC QLQ-C30 and EORTC QLQ-BR23 at 1 year.

3.2.2.4. IMRT PBI Versus WBI

Compared with WBI, IMRT was found to have no significant difference in IBR at 5 years and 10 years (low SOE), overall survival at 5 years and 10 years (low SOE), and provider-reported cosmesis at 5 years (insufficient SOE) and 10 years (insufficient SOE). Patient-reported cosmesis was significantly better among patients treated with IMRT than WBI at 10 years in one RCT (RR: 0.05; 95% CI: 0.01 to 0.22; I^2= N/A, low SOE).[24, 58-61] There was no significant difference in acute and late AEs, contralateral breast cancer recurrence, distant breast cancer recurrence, tumor bed IBR, and elsewhere IBR at 5 years and 10 years. The Florence trial reported that, compared with WBI, IMRT accelerated partial breast irradiation (APBI) was associated with significantly better quality of life (global health status, functional and symptom) measured by EORTC QLQ-C30 scales and symptom scales (breast and arm symptoms) measured by EORTC QLQ-BR23 at 2 years.[58]

3.2.2.5. Multi-Catheter Interstitial Brachytherapy Versus WBI

There was no significant difference between multi-catheter interstitial brachytherapy and WBI in IBR, overall survival, and cancer-free survival at 5 years (low SOE). Multi-catheter interstitial brachytherapy was found to be associated with significantly less incidence of acute AEs and acute AEs grade 2 or above, and no difference in late AEs, contralateral breast cancer recurrence at 5 years and distant breast cancer recurrence at 5 years. There was insufficient evidence in patient and provider reported cosmesis at 5 years. Multi-catheter interstitial brachytherapy was associated with better breast symptoms and arm symptoms after radiation therapy, 3-month followup and 5-year followup (measured by EORTC QLQ-BR23).[55] There was not significant difference on global health status at 5 years (measured by EORTC QLQ-C30).

Table 5. KQ 1. Main outcomes: PBI versus WBI

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
PBI compared with WBI†	IBR	5 years	RR: 1.34; 95% CI: 0.83 to 2.18; I^2= 0%; RD: 0.00; 95% CI: 0.00 to 0.01 PBI: 0.02% (55/2990) vs. WBI: 0.01% (41/3008)	8 RCTs,[22-25, 40, 52-61, 64-71] 5,998 patients	No difference	High

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
PBI compared with WBI (continued)	IBR	10 years	RR: 1.29; 95% CI: 0.87 to 1.91; I^2= 0%; RD: 0.01; 95% CI: 0.00 to 0.02 PBI: 4.01% (143/3565) vs. WBI: 3.11% (111/3564)	4 RCTs,[21, 22, 24, 52, 53, 58-61, 66-70] 7,129 patients	No difference	High
	IBR	> 10 years	RR: 1.20; 95% CI: 0.01 to 177.35; I^2= 0%; RD: 0.01; 95% CI: -0.27 to 0.28 PBI: 7.26% (13/179) vs. WBI: 6.08% (11/181)	2 RCTs,[64-70] 360 patients	No difference	Insufficient (Rated down 3 times for imprecision)
	Overall survival	5 years	RR: 1.00; 95% CI: 0.99 to 1.01; I^2= 0%; RD: 0.00; 95% CI: -0.01 to 0.01 PBI: 95.85% (2817/2939) vs. WBI: 96.04% (2840/2957)	7 RCTs,[22-25, 40, 52-61, 66-71] 5,876 patients	No difference	High
	Overall survival	10 years	RR: 1.01; 95% CI: 0.97 to 1.04; I^2= 28.73%; RD: 0.01; 95% CI; -0.02 to 0.03 PBI: 90.72% (3234/3565) vs WBI: 89.84% (3202/3564)	4 RCTs,[21, 22, 24, 52, 53, 58-61, 66-70] 7,129 patients	No difference	High
	Overall survival	> 10 years	RR: 1.00; 95% CI: 0.45 to 2.20; I^2= 0%; RD: 0.00; 95% CI: -0.58 to 0.57 PBI: 67.04% (120/179) vs. WBI: 67.40% (122/181)	2 RCTs,[64-70] 360 patients	No difference	Insufficient (Rated down 3 levels for imprecision)
	Cancer-free survival	5 years	RR: 1.00; 95% CI: 0.98 to 1.02; I^2= 0%; RD: 0.00; 95% CI: -0.02 to 0.02 PBI: 92.44% (2336/2527) vs. WBI: 92.75% (2353/2537)	4 RCTs,[22, 23, 25, 52-57, 66-70] 5,064 patients	No difference	High

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
PBI compared with WBI (continued)	Cancer-free survival	10 years	RR: 0.97; 95% CI: 0.92 to 1.02; I^2= 0%; RD: -0.03 95% CI: -0.07 to 0.01 PBI: 80.12% (2648/3305) vs. WBI: 87% 82.(2738/3304)	3 RCTs,[21, 22, 52, 53, 66-70] 6,609 patients	No difference	High
	Cancer-free survival	>10 years	RR: 1.01; 95% CI: 0.53 to 1.94; I^2= 0%; RD: 0.01; 95% CI: -0.52 to 0.53 PBI: 81.01% (145/179) vs. WBI: 80.11% (145/181)	2 RCTs,[64-70] 360 patients	No difference	Insufficient (Rated down 3 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 0.82; 95% CI: 0.35 to 1.94; I^2= 89%; RD: -0.01; 95% CI: -0.13 to 0.10 PBI: 15.84% (366/2311) vs. WBI: 10.83% (253/2336)	7 RCTs,[22-24, 40, 51-53, 55-61, 64-70] 4,647 patients	No difference	Insufficient (Risk of bias, inconsistency, and rated down 1 level for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	10 years	RR: 0.80; 95% CI: 0.03 to 19.56; I^2= 94%; RD: 0.00; 95% CI: -0.33 to 0.32 PBI: 18.86% (275/1458) vs. WBI: 11.34% (165/1455)	3 RCTs,[22, 24, 52, 53, 58-61, 66-70] 2,913 patients	No difference	Insufficient (Risk of bias, inconsistency, and rated down 1 level for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	> 10 years	RR: 0.56; 95% CI: 0.37 to 0.85; I^2= N/A; RD: -0.16; 95% CI: -0.27 to -0.05 PBI: 20.31% (26/128) vs. WBI: 36.15% (47/130)	1 RCT,[66-70] 258 patients	Favors PBI	Low (Risk of bias, and rated down 1 level for imprecision)
	Cosmesis reported by patient (poor or fair)	5 years	RR: 1.44; 95% CI: 0.58 to 3.59; I^2= 56%; RD: 0.04; 95% CI: -0.10 to 0.19 PBI: 16.78% (298/1776) vs. WBI: 10.34 (185/1789)	3 RCTs,[22, 23, 52, 53, 55-57, 64, 65] 3,565 patients	No difference	Insufficient (Risk of bias, inconsistency, and rated down 1 level for imprecision)

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
PBI compared with WBI (continued)	Cosmesis reported by patient (poor or fair)	10 years	RR: 0.37; 95% CI: 0 to +∞; I^2= 96%; RD: -0.01; 95% CI: -0.61 to 1.59 PBI: 16.24% (216/1330) vs. WBI: 9.81% (130/1325)	2 RCTs,[22, 24, 52, 53, 58-61] 2,655 patients	No difference	Insufficient (Risk of bias, inconsistency, and rated down 1 level for imprecision)
	Total AE	Acute	IRR: 0.53; 95% CI: 0.31 to 0.92; I^2= 88%* PBI: 45.53% (994/2183) vs. WBI: 75.61% (1668/2206)	6 RCTs,[22-24, 40, 51-53, 55-61, 64, 65] 4,389 patients	Favors PBI	Moderate (Inconsistency)
	Total AE	Late	IRR: 0.85; 95% CI: 0.44 to 1.62; I^2= 97% PBI: 71.63% (3644/5087) vs. WBI: 69.76% (3571/5119)	9 RCTs,[21-25, 40, 51-61, 64-70] 10,206 patients	No difference	Moderate (Inconsistency)
IORT compared with WBI	IBR	5 years	RR: 3.92; 95% CI: 2.44 to 6.32; I^2= 74.14%; RD: 0.03; 95% CI: 0.02 to 0.03* IORT: 3.46% (82/2372) vs. WBI: 0.88% (21/2384)	2 RCTs,[41-50, 62, 63] 4,756 patients	Favors WBI	High
	IBR	10 years	RR: 7.61; 95% CI: 3.48 to 16.60; I^2= N/A; RD: 0.07; 95% CI: 0.05 to 0.09 IORT: 8.14% (53/651) vs. WBI: 1.07% (7/654)	1 RCT,[62, 63] 1,305 patients	Favors WBI	High
	IBR	> 10 years	RR: 4.40; 95% CI: 2.58 to 7.48; I^2= N/A; RD: 0.08; 95% CI: 0.06 to 0.11 IORT: 10.75% (70/651) vs. WBI: 2.45% (16/654)	1 RCT,[62, 63] 1,305 patients	Favors WBI	High
	Overall survival	5 years	RR: 1.00; 95% CI: 0.93 to 1.08; I^2= 0%; RD: 0.00; 95% CI: -0.07 to 0.07 IORT: 95.99% (2277/2372) vs. WBI: 95.81% (2284/2384)	2 RCTs,[41-50, 62, 63] 4,756 patients	No difference	High

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
IORT compared with WBI (continued)	Overall survival	10 years	RR: 0.98; 95% CI: 0.95 to 1.01; I^2= N/A; RD: -0.02; 95% CI: -0.05 to 0.01 IORT: 90.63% (590/651) vs. WBI: 92.66% (606/654)	1 RCT,[62, 63] 1,305 patients	No difference	Low (Rated down 2 levels for imprecision)
	Overall survival	> 10 years	RR: 1.01; 95% CI: 0.88 to 1.15; I^2= 0%; RD: 0.01; 95% CI: -0.11 to 0.12 IORT: 88.49% (2099/2372) vs. WBI: 88.05% (2099/2384)	2 RCTs,[41-50, 62, 63] 4,756 patients	No difference	High
	Cancer-free survival	5 years	RR: 1.00; 95% CI: 0.97 to 1.02; I^2= N/A; RD: 0.00; 95% CI: -0.02 to 0.01 IORT: 90.53% (1558/1721) vs. WBI: 90.98% (1574/1730)	1 RCT,[41-50] 3,451 patients	No difference	High
	Mastectomy-free survival	5 years	RR: 0.97; 95% CI: 0.95 to 1.00; I^2=N/A; RD: -0.03; 95% CI: -0.05 to 0.00 IORT: 93.29% (542/581) vs. WBI: 95.98% (549/572)	1 RCT,[43] 1,153 patients	No difference	High
	Mastectomy-free survival	10 years	RR: 0.99; 95% CI: 0.94 to 1.03; I^2=N/A; RD: -0.01; 95% CI: -0.05 to 0.03 IORT: 85.89% (499/581) vs. WBI: 86.89% (497/572)	1 RCT,[43] 1,153 patients	No difference	Low (Rated down 2 levels for imprecision)
	Mastectomy-free survival	> 10 years	RR: 0.99; 95% CI: 0.97 to 1.02; I^2= N/A; RD: -0.01; 95% CI: -0.03 to 0.02 IORT: 84.78% (1459/1721) vs. WBI: 85.32% (1476/1730)	1 RCT,[41-50] 3,451 patients	No difference	High

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
3DCRT compared with WBI	IBR	5 years	RR: 1.14; 95% CI: 0.50 to 2.61; I^2= 0%; RD: 0.00; 95% CI: -0.01 to 0.01 3DCRT: 1.66% (31/1865) vs. WBI: 1.46% (27/1855)	4 RCTs,[22, 25, 52-54, 64, 65, 71] 3,720 patients	No difference	Moderate (Rated down 1 level for imprecision)
	IBR	10 years	RR: 1.32; 95% CI: 0.81 to 2.13; I^2= N/A; RD: 0.01; 95% CI: -0.01 to 0.02 3DCRT: 3.46% (37/1070) vs. WBI: 2.63% (28/1065)	1 RCT,[22, 52, 53] 2,135 patients	No difference	Moderate (Rated down 1 level for imprecision)
	IBR	> 10 years	RR: 1.00; 95% CI: 0.06 to 15.56; I^2= N/A; RD: 0.00, 95% CI: -0.05 to 0.05 3DCRT: 1.96% (1/51) vs. WBI: 1.96% (1/51)	1 RCT,[64, 65] 102 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Overall survival	5 years	RR: 0.99; 95% CI: 0.97 to 1.02; I^2= 0%; RD: -0.01; 95% CI: -0.04 to 0.02 3DCRT: 95.42% (1731/1814) vs. WBI: 96.29% (1737/1804)	3 RCTs,[22, 25, 52-54, 71] 3,618 patients	No difference	High
	Overall survival	10 years	RR: 0.99; 95% CI: 0.97 to 1.01; I^2= N/A; RD: -0.01; 95% CI: -0.03 to 0.01 3DCRT: 92.90% (994/1070) vs. WBI: 93.99% (1001/1065)	1 RCT,[22, 52, 53] 2,135 patients	No difference	High
	Overall survival	> 10 years	RR: 1.00; 95% CI: 0.86 to 1.17; I^2= N/A; RD: 0.00; 95% CI: -0.13 to 0.13 3DCRT: 86.27% (44/51) vs. WBI: 86.27% (44/51)	1 RCT,[64, 65] 102 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Cancer-free survival	5 years	RR: 0.99; 95% CI: 0.88 to 1.12; I^2= 0%; RD: -0.01; 95% CI: -0.12 to 0.11 3DCRT: 91.57% (1597/1744) vs, WBI: 92.27% (1600/1734)	2 RCT,[22, 25, 52-54] 3,478 patients	No difference	High

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
3DCRT compared with WBI (continued)	Cancer-free survival	10 years	RR: 0.97; 95% CI: 0.93 to 1.01; I^2=N/A; RD: -0.03; 95% CI: -0.06 to 0.01 3DCRT: 81.40% (871/1070) vs. WBI: 84.04% (895/1065)	1 RCT,[22, 52, 53] 2,135 patients	No difference	High
	Cancer-free survival	> 10 years	RR: 1.00; 95% CI: 0.85 to 1.18; I^2= N/A; RD: 0.00; 95% CI: -0.14 to 0.14 3DCRT: 84.31% (43/51) vs. WBI:84.31% (43/51)	1 RCT,[64, 65] 102 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 1.01; 95% CI: 0.03 to 31.89; I^2= 91%; RD: 0.00; 95% CI: -0.57 to 0.57 3DCRT: 25.04% (297/1186) vs. WBI: 13.36% (158/1183)	3 RCTs,[22, 51-53, 64, 65] 2,369 patients	No difference	Insufficient (Risk of bias, rated down 1 level for imprecision, and inconsistency)
	Cosmesis reported by healthcare provider (poor or fair)	10 years	RR: 2.14; 95% CI: 1.74 to 2.61; I^2=N/A; RD: 0.12; 95% CI: 0.09 to 0.16 3DCRT: 23.46% (251/1070) vs. WBI: 10.99% (117/1065)	1 RCT,[22, 52, 53] 2,135 patients	Favors WBI	Moderate (Risk of bias)
	Cosmesis reported by patient (poor or fair)	5 years	RR: 1.76; 95% CI: 0.53 to 5.87; I^2= 0%; RD: 0.10; 95% CI: -0.11 to 0.32 3DCRT: 22.75% (255/1121) vs. WBI: 12.90% (144/1116)	2 RCT,[22, 52, 53, 64, 65] 2,237 patients	No difference	Low (Risk of bias, and rated down 1 level for imprecision)
	Cosmesis reported by patient (poor or fair)	10 years	RR: 2.32; 95% CI: 1.84 to 2.91; I^2=N/A; RD: 0.11; 95% CI: 0.08 to 0.14 3DCRT: 20% (214/1070) vs. WBI: 8.64% (92/1065)	1 RCT,[22, 52, 53] 2,135 patients	Favors WBI	Moderate (Risk of bias)

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
IMRT compared with WBI	IBR	5 years	RR: 1.86; 95% CI: 0.00 to +∞; I^2= 0%; RD: 0.01; 95% CI: -0.12 to 0.14 IMRT: 2.63% (9/342) vs. WBI: 1.43% (5/350)	2 RCTs,[24, 40, 58-61] 692 patients	No difference	Low (Rated down 2 levels for imprecision)
	IBR	10 years	RR: 1.50; 95% CI: 0.54 to 4.15; I^2= N/A; RD: 0.01;95% CI: -0.02 to 0.04 IMRT: 3.46% (9/260) vs. WBI: 2.31% (6/260)	1 RCT,[24, 58-61] 520 patients	No difference	Low (Rated down 2 levels for imprecision)
	Overall survival	5 years	RR: 1.00; 95% CI: 0.90 to 1.13; I^2= 0%; RD: 0.01; 95% CI: -0.16 85 to 0.19 IMRT: 98.54% (337/342) vs. WBI: 97.71% (342/350)	2 RCTs,[24, 40, 58-61] 692 patients	No difference	Low (Rated down 2 levels for imprecision)
	Overall survival	10 years	RR: 1.01; 95% CI: 0.96 to 1.06; I^2= N/A; RD: 0.01; 95% CI: -0.04 to 0.05 IMRT: 93.08% (242/260) vs. WBI: 92.31% (240/260)	1 RCT,[24, 58-61] 520 patients	No difference	Low (Rated down 2 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 0.43; 95% CI: 0.00 to +∞; I^2= 0%; RD: -0.01; 95% CI: -0.08 to 0.06 IMRT: 0.58% (2/342) vs. WBI: 1.71% (6/350)	2 RCTs,[24, 40, 58-61] 692 patients	No difference	Insufficient (Risk of bias, and rated down 2 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	10 years	RR: 0.09; 95% CI: 0.01 to 1.64; I^2= N/A; RD: -0.02; 95% CI: -0.04 to 0.00 IMRT: 0% (0/260) vs. WBI: 1.92% (5/260)	1 RCT,[24, 58-61] 520 patients	No difference	Insufficient (Risk of bias, and rated down 2 level for imprecision)
	Cosmesis reported by patient (poor or fair)	10 years	RR: 0.05; 95% CI: 0.01 to 0.22; I^2= N/A; RD: -0.14; 95% CI: -0.24 to -0.03 IMRT: 0.77% (2/260) vs. WBI: 14.62% (38/260)	1 RCT,[24, 58-61] 520 patients	Favors IMRT	Low (Risk of bias, and rated down 1 level for imprecision)

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
Multi-catheter interstitial brachytherapy compared with WBI	IBR	5 years	RR: 1.85; 95% CI: 0.62 to 5.49; I^2= N/A; RD: 0.01; 95% CI: 0.00 to 0.02 Multi-catheter interstitial brachytherapy: 1.37% (9/655) vs. WBI: 0.74% (5/673)	1 RCT,[23, 55-57] 1,328 patients	No difference	Low (Rated down 2 levels for imprecision)
	Overall survival	5 years	RR: 1.01; 95% CI: 0.98 to 1.03; I^2= N/A; RD: 0.01; 95% CI: -0.02 to 0.03 Multi-catheter interstitial brachytherapy: 95.88% (628/655) vs. WBI: 95.25% (641/673)	1 RCT,[23, 55-57] 1,328 patients	No difference	Low (Rated down 2 levels for imprecision)
	Cancer-free survival	5 years	RR: 1.00; 95% CI: 0.98 to 1.03; I^2= N/A; RD: 0.00; 95% CI: -0.02 to 0.03 Multi-catheter interstitial brachytherapy: 94.96% (622/655) vs. WBI: 94.50% (636/673)	1 RCT,[23, 55-57] 1,328 patients	No difference	Low (Rated down 2 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 0.87; 95% CI: 0.58 to 1.32; I^2= N/A; RD: -0.01; 95% CI: -0.04 to 0.02 Multi-catheter interstitial brachytherapy: 5.95% (39/655) vs. WBI: 6.84% (46/673)	1 RCT,[23, 55-57] 1,328 patients	No difference	Insufficient (Rated down 2 levels for imprecision, and risk of bias)
	Cosmesis reported by patient (poor or fair)	5 years	RR: 1.08; 95% CI: 0.71 to 1.63; I^2= N/A; RD: 0:00; 95% CI: -0.02 to 0:03 Multi-catheter interstitial brachytherapy: 6.56% (43/655) vs. WBI: 6.09% (41/673)	1 RCT,[23, 55-57] 1,328 patients	No difference	Insufficient (Rated down 2 levels for imprecision, and risk of bias)

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiotherapy; AE = adverse event; CI = confidence interval; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; IRR =

incidence rate ratio; KQ = Key Question; N/A = not applicable; PBI = partial breast irradiation; RCT = randomized clinical trial; RD = risk difference; RR = relative risk; SOE = strength of evidence; WBI = whole breast irradiation

* Results are statistically significant at two tailed $p<0.05$.

†Although a few smaller trials had high risk of bias, the five largest trials had low risk of bias and there was no difference in estimates based on risk of bias.

Table 6. KQ 1. Secondary outcomes

Comparison	Outcome	Time	Findings	Direction of Effect	Study Design and Sample Size
PBI compared with WBI	AE grade ≥ 2	Acute	IRR: 0.21; 95% CI: 0.07 to 0.62; I^2= 94%* PBI: 16.63% (363/2183) vs. WBI: 40.93% (903/2206)	Favors PBI	6 RCTs,[22-24, 40, 51-53, 55-61, 64, 65] 4,389 patients
	AE grade ≥ 2	Late	IRR: 0.75; 95% CI: 0.28 to 2.03; I^2= 96% PBI: 38.76% (1562/4030) vs. WBI: 39.73% (1611/4055)	No difference	6 RCTs,[21-23, 40, 51-53, 55-57, 64, 65] 8,085 patients
	Tumor bed IBR	5 years	RR: 0.67; 95% CI: 0.17 to 2.56; I^2= 0%; RD: -0.01; 95% CI: -0.02 to 0.01 PBI: 0.81% (9/1113) vs. WBI: 1.26% (14/1110)	No difference	4 RCTs,[24, 25, 54, 58-61, 64-70] 2,223 patients
	Tumor bed IBR	10 years	RR: 0.89; 95% CI: 0.27 to 2.89; I^2= 0%; RD: 0.00; 95% CI: -0.02 to 0.02 PBI: 1.71% (25/1458) vs. WBI: 1.92% (28/1455)	No difference	3 RCTs,[22, 24, 52, 53, 58-61, 66-70] 2,913 patients
	Tumor bed IBR	> 10 years	RR: 0.85; 95% CI: 0.26 to 2.70; I^2= N/A; RD: -0.01; 95% CI: -0.06 to 0.04 PBI: 3.91% (5/128) vs. WBI: 4.62% (6/130)	No difference	1 RCT,[66-70] 258 patients
	Elsewhere IBR	5 years	RR: 1.52; 95% CI: 0.19 to 12.43; I^2= 0%; RD: 0.00; 95% CI: -0.01 to 0.00 PBI: 0.54% (6/1113) vs. WBI: 0.27% (3/1110)	No difference	4 RCTs,[24, 25, 54, 58-61, 64-70] 2,223 patients
	Elsewhere IBR	10 years	RR: 2.33; 95% CI: 0.53 to 10.19; I^2= 0%; RD: 0.01; 95% CI: -0.01 to 0.03 PBI: 1.92% (28/1458) vs. WBI: 0.82% (12/1455)	No difference	3 RCTs,[22, 24, 52, 53, 58-61, 66-70] 2,913 patients
	Elsewhere IBR	>10 years	RR: 1.63; 95% CI: 0.55 to 4.83; I^2= N/A; RD: 0.02; 95% CI: -0.03 to 0.08 PBI: 6.25% (8/128) vs. WBI: 3.85% (5/130)	No difference	1 RCT,[66-70] 258 patients
	Contralateral breast cancer recurrence	5 years	RR: 1.06; 95% CI: 0.43 to 2.58; I^2= 15%; RD: 0.00; 95% CI: -0.01 to 0.01 PBI: 1.56% (28/1799) vs. WBI: 1.48% (27/1822)	No difference	5 RCTs,[23-25, 40, 54-61, 66-70] 3,621 patients

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Direction of Effect	Study Design and Sample Size
PBI compared with WBI (continued)	Contralateral breast cancer recurrence	10 years	RR: 0.74; 95% CI: 0.19 to 2.86; I^2= 26%; RD: -0.01; 95% CI: -0.04 to 0.02 PBI: 2.67% (39/1458) vs. WBI: 3.64% (53/1455)	No difference	3 RCTs,[22, 24, 52, 53, 58-61, 66-70] 2,913 patients
	Contralateral breast cancer recurrence	> 10 years	RR: 0.53; 95% CI: 0.26 to 1.10; I^2= N/A; RD: -0.07; 95% CI: -0.14 to 0.01 PBI: 7.81% (10/128) vs. WBI: 14.62% (19/130)	No difference	1 RCT,[66-70] 258 patients
	Distant breast cancer recurrence	5 years	RR: 0.92; 95% CI: 0.48 to 1.74; I^2= 0%; RD: 0.00; 95% CI: -0.01 to 0.01 PBI: 1.57% (29/1850) vs. WBI: 1.71% (32/1873)	No difference	6 RCTs,[23-25, 40, 54-61, 64-70] 3,723 patients
	Distant breast cancer recurrence	10 years	RR: 0.92; 95% CI: 0.35 to 2.45; I^2= 0%; RD: 0.00; 95% CI: -0.02 to 0.02 PBI: 2.47% (36/1458) vs. WBI: 2.68% (39/1455)	No difference	3 RCTs,[22, 24, 52, 53, 58-61, 66-70] 2,913 patients
	Distant breast cancer recurrence	> 10 years	RR: 0.80; 95% CI: 0.43 to 1.51; I^2= N/A; RD: -0.03; 95% CI: -0.11 to 0.05 PBI: 11.72% (15/128) vs. WBI: 14.62% (19/130)	No difference	1 RCT,[66-70] 258 patients
IORT compared with WBI	Total AE	Acute	IRR: 0.16; 95% CI: 0.06 to 0.40; I^2= N/A* IORT: 0.77% (5/651) vs. WBI: 4.89% (32/654)	Favors IORT	1 RCT,[62, 63] 1,305 patients
	Total AE	Late	IRR: 1.00; 95% CI: 0.59 to 1.71; I^2= 0% IORT: 47.18% (1119/2372) vs. WBI: 47.15% (1124/2384)	No difference	2 RCTs,[41-50, 62, 63] 4,756 patients
	AE grade ≥ 2	Late	IRR: 0.26; 95% CI: 0.11 to 0.64; I^2= N/A* IORT: 0.35% (6/1721) vs. WBI: 1.33% (23/1730)	Favors IORT	1 RCT,[41-50] 3,451 patients
	Tumor bed IBR	5 years	RR: 5.27; 95% CI: 1.82 to 15.28; I^2=N/A; RD: 0.03; 95% CI: 0.01 to 0.04 IORT: 3.23% (21/651) vs. WBI: 0.61% (4/654)	Favors WBI	1 RCT,[62, 63] 1,305 patients
	Elsewhere IBR	5 years	RR: 29.13; 95% CI: 1.74 to 487.36; I^2= N/A; RD: 0.02; 95% CI: 0.01 to 0.03 IORT: 2.15% (14/651) vs. WBI: 0% (0/654)	Favors WBI	1 RCT,[62, 63] 1,305 patients
	Contralateral breast cancer recurrence	5 years	RR: 0.62; 95% CI: 0.26 to 1.48; I^2= N/A; RD: -0.01; 95% CI: -0.02 to 0.01 IORT: 1.23% (8/651) vs. WBI: 1.99% (13/654)	No difference	1 RCT,[62, 63] 1,305 patients
	Contralateral breast cancer recurrence	10 years	RR: 0.50; 95% CI: 0.24 to 1.06; I^2= N/A; RD: -0.02; 95% CI: -0.03 to 0.00 IORT: 1.54% (10/651) vs. WBI: 3.06% (20/654)	No difference	1 RCT,[62, 63] 1,305 patients

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Direction of Effect	Study Design and Sample Size
IORT compared with WBI (continued)	Contralateral breast cancer recurrence	> 10 years	RR: 0.67; 95% CI: 0.37 to 1.20; I^2= N/A; RD: -0.01; 95% CI: -0.03 to 0.01 IORT: 2.76% (18/651) vs. WBI: 4.13% (27/654)	No difference	1 RCT,[62, 63] 1,305 patients
	Distant breast cancer recurrence	5 years	RR: 0.95; 95% CI: 0.60 to 1.50; I^2= N/A; RD: 0.00; 95% CI: -0.03 to 0.02 IORT: 5.07% (33/651) vs. WBI: 5.35% (35/654)	No difference	1 RCT,[62, 63] and 1,305 patients
	Distant breast cancer recurrence	10 years	RR: 0.80; 95% CI: 0.53 to 1.20; I^2= N/A; RD: -0.02; 95% CI: -0.04 to 0.01 IORT: 5.99% (39/651) vs. WBI: 7.49% (49/654)	No difference	1 RCT,[62, 63] 1,305 patients
	Distant breast cancer recurrence	> 10 years	RR: 0.86; 95% CI: 0.59 to 1.25; I^2= N/A; RD: -0.01; 95% CI: -0.04 to 0.02 IORT: 7.07% (46/651) vs. WBI: 8.26% (54/654)	No difference	1 RCT,[62, 63] 1,305 patients
3DCRT compared with WBI	Total AE	Acute	IRR: 0.69; 95% CI: 0.34 to 1.40; I^2= 62% 3DCRT: 37.52% (445/1186) vs. WBI: 62.55% (740/1183)	No difference	3 RCTs,[22, 51-53, 64, 65] 2,369 patients
	Total AE	Late	IRR: 1.13; 95% CI: 0.23 to 5.48; I^2= 99% 3DCRT: 53.64% (995/1855) vs. WBI: 45.34% (842/1857)	No difference	4 RCTs,[22, 25, 51-54, 64, 65] 3,712 patients
	AE grade ≥ 2	Acute	IRR: 0.44; 95% CI: 0.11 to 1.84; I^2= 69% 3DCRT: 26.48% (314/1186) vs. WBI: 44.97% (532/1183)	No difference	3 RCTs,[22, 51-53, 64, 65] 2,369 patients
	AE grade ≥ 2	Late	IRR: 0.55; 95% CI: 0.01 to 46.44; I^2= 94% 3DCRT: 29.76% (353/1186) vs. WBI: 14.88% (176/1183)	No difference	3 RCTs,[22, 51-53, 64, 65] 2,369 patients
	Tumor bed IBR	5 years	RR: 0.47; 95% CI: 0.00 to 686.34; I^2= 0%; RD: -0.01; 95% CI: -0.08 to 0.06 3DCRT: 0.55% (4/725) vs. WBI: 1.25% (9/720)	No difference	2 RCTs,[25, 54, 64, 65] 1,445 patients
	Tumor bed IBR	10 years	RR: 0.85; 95% CI: 0.45 to 1.61; I^2=N/A; RD: 0.00; 95% CI: -0.01 to 0.01 3DCRT: 1.59% (17/1070) vs. WBI: 1.88% (20/1065)	No difference	1 RCT,[22, 52, 53] 2,135 patients
	Elsewhere IBR	5 years	RR: 0.52; 95% CI: 0.00 to +∞; I^2= 0%; RD: 0.00; 95% CI: -0.02 to 0.02 3DCRT: 0% (0/725) vs. WBI: 0.14% (1/720)	No difference	2 RCTs,[25, 54, 64, 65] 1,445 patients

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Direction of Effect	Study Design and Sample Size
3DCRT compared with WBI (continued)	Elsewhere IBR	10 years	RR: 2.49; 95% CI: 1.10 to 5.62; I^2=N/A; RD: 0.01; 95% CI: 0.00 to 0.02 3DCRT: 1.87% (20/1070) vs. WBI: 0.75% (8/1065)	Favors WBI	1 RCT,[22, 52, 53] 2,135 patients
	Contralateral breast cancer recurrence	5 years	RR: 1.08; 95% CI: 0.49 to 2.34; I^2= N/A; RD: 0.00; 95% CI: -0.01 to 0.02 3DCRT: 1.93% (13/674) vs. WBI: 1.79% (12/669)	No difference	1 RCT,[25, 54] 1,343 patients
	Contralateral breast cancer recurrence	10 years	RR: 0.76; 95% CI: 0.47 to 1.22; I^2=N/A; RD: -0.01; 95% CI: -0.02 to 0.01 3DCRT: 2.71% (29/1070) vs. WBI: 3.57% (38/1065)	No difference	1 RCT,[22, 52, 53] 2,135 patients
	Distant breast cancer recurrence	5 years	RR: 0.92; 95% CI: 0.01 to 128.74; I^2= 0%; RD: 0.00; 95% CI: -0.10 to 0.09 3DCRT: 1.66% (12/725) vs. WBI: 1.81% (13/720)	No difference	2 RCTs,[25, 54, 64, 65] 1,445 patients
	Distant breast cancer recurrence	10 years	RR: 1.11; 95% CI: 0.59 to 2.08; I^2=N/A; RD: 0.00; 95% CI: -0.01 to 0.01 3DCRT: 1.87% (20/1070) vs. WBI: 1.69% (18/1065)	No difference	1 RCT, [22, 52, 53] 2,135 patients
IMRT compared with WBI	Total AE	Acute	IRR: 0.28; 95% CI: 0.05 to 1.73; I^2= 0% IMRT: 18.42% (63/342) vs. WBI: 65.43% (229/350)	No difference	2 RCTs,[24, 40, 58-61] 692 patients
	Total AE	Late	IRR: 0.26; 95% CI: 0.00 to 223.07; I^2= 83% IMRT: 7.89% (27/342) vs. WBI: 32.86% (115/350)	No difference	2 RCTs,[24, 40, 58-61] 692 patients
	AE grade ≥ 2	Acute	IRR: 0.05; 95% CI: 0.00 to 10.98; I^2= 0% IMRT: 1.75% (6/342) vs. WBI: 32.57% (114/350)	No difference	2 RCTs,[24, 40, 58-61] 692 patients
	AE grade ≥ 2	Late	IRR: 0.27; 95% CI: 0.03 to 2.45; I^2= N/A IMRT: 1.22% (1/82) vs. WBI: 4.44% (4/90)	No difference	1 RCT,[40] 172 patients
	Tumor bed IBR	5 years	RR: 1.00; 95% CI: 0.20 to 4.91; I^2= N/A; RD: 0.00; 95% CI: -0.02 to 0.02 IMRT: 1.15% (3/260) vs. WBI: 1.15% (3/260)	No difference	1 RCT,[24, 58-61] 520 patients
	Tumor bed IBR	10 years	RR: 1.25; 95% CI: 0.34 to 4.60; I^2= N/A; RD: 0.00; 95% CI: -0.02 to 0.03 IMRT: 1.92% (5/260) vs. WBI: 1.54% (4/260)	No difference	1 RCT,[24, 58-61] 520 patients
	Elsewhere IBR	5 years	RR: 7.00; 95% CI: 0.36 to 134.84; I^2= N/A; RD: 0.01; 95% CI: 0.00 to 0.02 IMRT: 1.15% (3/260) vs. WBI: 0% (0/260)	No difference	1 RCT,[24, 58-61] 520 patients

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Direction of Effect	Study Design and Sample Size
IMRT compared with WBI (continued)	Elsewhere IBR	10 years	RR: 2.00; 95% CI: 0.37 to 10.82; I^2= N/A; RD: 0.01; 95% CI: -0.01 to 0.03 IMRT: 1.54% (4/260) vs. WBI: 0.78% (2/260)	No difference	1 RCT,[24, 58-61] 520 patients
	Contralateral breast cancer recurrence	5 years	RR: 0.34; 95% CI: 0.00 to +∞; I^2= 0%; RD: -0.02; 95% CI: -0.16 to 0.13 IMRT: 0.58% (2/342) vs. WBI: 2% (7/350)	No difference	2 RCTs,[24, 40, 58-61] 692 patients
	Contralateral breast cancer recurrence	10 years	RR: 0.25; 95% CI: 0.05 to 1.17; I^2= N/A; RD: -0.02; 95% CI: -0.05 to 0.00 IMRT: 0.77% (2/260) vs. 3.08% (8/260)	No difference	1 RCT,[24, 58-61] 520 patients
	Distant breast cancer recurrence	5 years	RR: 0.70; 95% CI: 0.00 to +∞; I^2= 0%; RD: -0.01; 95% CI: -0.16 to 0.15 IMRT: 1,17% (4/342) vs. WBI: 1.71% (6/350)	No difference	2 RCTs,[24, 40, 58-61] 692 patients
	Distant breast cancer recurrence	10 years	RR: 0.88; 95% CI: 0.32 to 2.38; I^2= N/A; RD: 0.00; 95% CI: -0.03 to 0.02 IMRT: 2.69% (7/260) vs. WBI: 3.08% (8/260)	No difference	1 RCT,[24, 58-61] 520 patients
Multi-catheter interstitial brachytherapy compared with WBI	Total AE	Acute	IRR: 0.71; 95% CI: 0.64 to 0.80; I^2= N/A* Multi-catheter interstitial brachytherapy: 74.20% (486/655) vs. WBI: 103.86% (699/673)	Favors multi-catheter interstitial brachytherapy	1 RCT,[23, 55-57] 1,328 patients
	Total AE	Late	IRR: 1.01; 95% CI: 0.89 to 1.13; I^2= N/A Multi-catheter interstitial brachytherapy: 80.46% (527/655) vs. WBI: 79.94% (538/673)	No difference	1 RCT,[23, 55-57] 1,328 patients
	AE grade ≥ 2	Acute	IRR: 0.17; 95% CI: 0.12 to 0.24; I^2= N/A* Multi-catheter interstitial brachytherapy: 6.56% (43/655) vs. WBI: 38.19% (257/673)	Favors multi-catheter interstitial brachytherapy	1 RCT,[23, 55-57] 1,328 patients
	AE grade ≥ 2	Late	IRR: 0.88; 95% CI: 0.65 to 1.19; I^2= N/A Multi-catheter interstitial brachytherapy: 11.60% (76/655) vs. WBI: 13.22% (89/673)	No difference	1 RCT,[23, 55-57] 1,328 patients
	Contralateral breast cancer recurrence	5 years	RR: 1.03; 95% CI: 0.30 to 3.53; I^2= N/A; RD: 0.00; 95% CI: -0.01 to 0.01 Multi-catheter interstitial brachytherapy: 0.76% (5/655) vs. WBI: 0.74% (5/673)	No difference	1 RCT,[23, 55-57] 1,328 patients

3.2.2. Results, Key Question 1: KQ 1 Results

Comparison	Outcome	Time	Findings	Direction of Effect	Study Design and Sample Size
Multi-catheter interstitial brachytherapy compared with WBI (continued)	Distant breast cancer recurrence	5 years	RR: 1.03; 95% CI: 0.30 to 3.53; I^2= N/A; RD: 0.00; 95% CI: -0.01 to 0.01 Multi-catheter interstitial brachytherapy: 0.76% (5/655) vs. WBI: 0.74% (5/673)	No difference	1 RCT,[23, 55-57] 1,328 patients

Abbreviations: ∞ = infinity; 3DCRT = 3-dimensional conformal external beam radiotherapy; AE = adverse event; CI = confidence interval; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; IRR = incidence rate ratio; KQ = Key Question; N/A = not applicable; PBI = partial breast irradiation; RCT = randomized clinical trial; RD = risk difference; RR = relative risk; WBI = whole breast irradiation

* Results are statistically significant at two tailed $p<0.05$.

3.2.2.6. PBI Effectiveness by Clinical-Pathologic Characteristics

Six original studies with 25 articles[21-24, 41-50, 52, 53, 55-63] provided sufficient data for subgroup analyses by clinical-pathologic characteristics (Appendix Tables J.1-J.21).

There was no significant difference in PBI effectiveness between subgroups as defined by age, disease stage, tumor grade, ER status, progesterone receptor (PR) status, Human Epidermal Growth Factor Receptor 2 (HER2) status, tumor histology, molecular subtype, resection margins, menopausal status, PBI suitability or invasive cancer risk group, tumor grade, lymphovascular invasion, Ki-67 proliferative index, lymph node status, adjuvant therapy, and intent to receive chemotherapy. Many studies specifically excluded patients with extensive intraductal component and there was insufficient data for analysis. In NSABP B-39,[21] researchers observed that, compared with invasive tumor size between 1 cm and 2 cm, tumors ≤1 cm were associated with significantly lower IBR at 10 years (RR: 0.54; 95% CI: 0.26 to 1.11 vs. RR: 2.79; 95% CI: 1.32 to 5.91).

Immediate IORT during lumpectomy as well as delayed IORT as a second procedure were each associated with a significantly higher rate of IBR at 5 years in comparison to WBI (RR: 2.22; 95% CI: 1.09 to 4.50 vs. RR: 3.77; 95% CI: 1.55 to 9.20); there was no difference in the comparison of immediate versus delayed IORT. The risk of IBR was higher with IORT than WBI in subgroups defined by age, histology, tumor size, nodal status, resection margins, tumor grade, ER status, PR status, Ki-67, HER2 status, and molecular subtype. In the ELIOT trial, the authors report a high rate of IBR among patients classified as being "suitable" for PBI according to American Society for Radiation Oncology (ASTRO) guidelines.[62, 63]

3.2.2.7. Effectiveness, Adverse Events, and Cosmetic Outcomes by Target Volumes, Dose-Fractionation Schemes, Motion Management, and Planning Parameters

Thirteen original studies with 38 articles provided sufficient data. For PBI with external beam radiotherapy (3DCRT or IMRT), the clinical target volume (CTV) was defined as a 1 cm expansion from the surgical bed or clips in four studies,[22, 24, 40, 51-53, 58-61] and a 1.5 cm expansion in two studies.[21, 25, 54] Surgical clips to demarcate the surgical bed were required as an eligibility criterion in one study[24, 58-61] and were required to define the clinical tumor volume in another study.[40] The planning target volume (PTV) was most commonly a 1 cm expansion from the CTV. Verification of treatment positioning was typically portal images and/or an orthogonal pair (anterior-posterior and lateral images); most studies did not require daily imaging.[21, 22, 24, 52, 53, 58-

[61] One study using a 0.5 cm PTV expansion required daily cone beam computed tomography (CT).[51] Motion management use was not reported.

The most commonly used dose and fractionation regimen for PBI was twice-daily treatment in 10 fractions, ranging from 34 Gy to 38.5 Gy in four clinical trials[21, 22, 51-53, 64, 65] involving 6,494 patients. Two clinical trials[24, 40, 58-61] with 692 patients evaluated treatment delivered every other day for a total of five treatments to a dose of 30 Gy. Nonaccelerated PBI was evaluated in three clinical trials,[25, 54, 67-70 37, 66] ranging from 40 Gy in 15 fractions to 55 Gy in 20 fractions.

For PBI with multi-catheter interstitial brachytherapy, two clinical trials,[23, 55-57, 67-70 66] delivered treatment using twice daily fractionation, ranging from 30.3 Gy in 7 fractions to 36.4 Gy in 7 fractions. Single lumen brachytherapy in one clinical trial delivered treatment twice-daily to 34 Gy in 10 fractions given twice daily. IORT delivered treatment in a single fraction to 20 Gy[41-50] or 21 Gy.[62, 63]

Appendix Table J.22 shows subgroup analyses by treatment schedule (accelerated PBI vs. nonaccelerated PBI). There was no significant difference between subgroups.
Appendix Table J.23 lists subgroup analyses by fractionation regimen. Twice daily fractionation was associated with significantly worse patient reported cosmesis (RR: 2.32; 95% CI: 1.84 to 2.91) and provider reported cosmesis (RR: 2.14; 95% CI: 1.74 to 2.61) at 10 years compared with fractionation of once every 2 days (patient reported cosmesis: RR: 0.05; 95% CI: 0.01 to 0.22; provider reported cosmesis: RR: 0.09; 95% CI: 0.01 to 1.64). Results for PBI with twice-daily fractionation and cosmesis were informed primarily by one large randomized trial using PBI delivered via external beam radiotherapy.[22] Twice daily fractionation was also associated with a significantly higher rate of acute AEs (RR: 0.69; 95% CI: 0.34 to 1.40) than once every 2 days (RR: 0.28; 95% CI: 0.21 to 0.38). There were no significant differences according to fractionation schedule for other outcome measures.

3.3. Key Question 2

3.3.1. KQ 2 Key Points

- Head-to-head comparisons between the different PBI modalities showed insufficient evidence to estimate an effect on main outcomes.
- These comparisons included IMRT versus 3DCRT, multi-catheter interstitial brachytherapy versus 3DCRT, proton versus 3DCRT, single-entry catheter brachytherapy versus 3DCRT, and single-entry catheter brachytherapy versus multi-catheter interstitial brachytherapy.

3.3.2. KQ 2 Results

Eleven studies reported in 19 articles were included in KQ 2 with a total of 2,362 patients who met inclusion criteria and were included for the analyses (Appendix B.). Of the 11 studies there were two RCTs,[66-70,72] six comparative observational studies[73-81] and three single-arm observational studies.[82-85] Average age of the patients were 61.83 years (range: 30-86) with average tumor size of 1.05 cm; 82.25 percent with tumor Grade 1 or 2; 6.17 percent with lobular cancer; 92.81 percent with no lymph node involvement; and 92.00 percent with positive estrogen receptor (ER). Eight studies were conducted in the United States,[72, 74, 79-85] and three in Europe.[66-70, 73, 75-78] The range of median followup was from 1 to 17 years.

These studies evaluated IMRT (1 RCT[72] and 1 comparative observational study[73]), proton radiotherapy (1 comparative observational study,[79] 3 single-arm observational studies[82-85]), IORT (1 comparative observational studies[75-78]), 3DCRT (2 RCTs,[66-70, 72] and 4 comparative observational studies[73, 74, 79, 80]), single-entry catheter brachytherapy (3 comparative observational studies [74, 80, 81]), multi-catheter interstitial brachytherapy (2 comparative observational studies[80, 81]), and multiple modalities (1 RCT (Budapest trial),[66-70] 1 comparative observational study[75-78])

The characteristics of included studies are in Appendix Table D.2.

3.3.2.1. IMRT Versus 3DCRT

One observational study[73] and one RCT[72] compared IMRT and 3DCRT.[73] The RCT with 656 patients found significantly greater cancer-free survival (low SOE) in the 3DCRT group than those in the IMRT group. There was no significant difference in IBR, overall survival, patient-reported cosmesis, and grade 3 and 4 AEs. The observational study reported no significant difference in IBR between IMRT and 3DCRT at 5 years, 10 years, or > 10 years. IMRT was associated with significantly worse cosmesis at 10 years when assessed by healthcare providers (RR: 0.05; 95% CI: 0.00 to 0.84; I^2=N/A) and patients (RR: 0.06; 95% CI: 0.00 to 0.98; I^2=N/A) and a statistically lower incidence of acute AEs (IRR: 0.54, 95% CI: 0.38 to 0.77; I^2=N/A).[73]. IMRT was associated with a lower risk for late AEs compared with 3DCRT (IRR: 0.46; 95% CI: 0.28 to 0.77; I^2=N/A). [73]

3.3.2.2. Multi-Catheter Interstitial Brachytherapy Versus 3DCRT

One observational study of 46 patients[80] and one RCT (Budapest trial) of 128 patients[66-70] compared multi-catheter interstitial brachytherapy with 3DCRT with insufficient SOE in all of the outcomes. There was no significant difference in overall survival at 5 years, IBR at 5 years, and poor or fair cosmesis reported by healthcare providers at 5 years 10 years or beyond 10

years.[66-70] There was no difference in total AEs between multi-catheter interstitial brachytherapy compared with 3DCRT.[66-70] There was no difference in distant breast cancer recurrence.[80]

3.3.2.3. Proton Versus 3DCRT

There were limited comparison data between proton PBI and 3DCRT. One observational study with 98 patients compared protons to 3DCRT.[79] As shown in Table 7, there was no significant difference in IBR between proton therapy and 3DCRT at 10 years. Proton therapy was associated with significantly more poor or fair cosmesis as evaluated by healthcare provider, compared with 3DCRT at 5 years and 10 years.[79] There was no statistical difference in patient reported poor or fair cosmesis at 5 years or 10 years.[79] The SOE is insufficient. Late AEs were higher among those treated with proton therapy, including skin effects and telangiectasia (Appendix Table I.2).

Three single-arm observational studies also evaluated proton APBI.[82-85] With 5 years of median followup, a single-arm proton APBI study of 100 patients reported 97 percent of patients were free of IBR at 5 years, and 90 percent of patients and providers assessed cosmesis as good to excellent with no change from baseline over the 5 years of followup. They reported no grade 3 or higher late toxicity and noted 7 percent telangiectasia.[84, 85] Pasalic et al[82] reported 100 percent of patients were alive without recurrence in the breast at 2 years among 100 patients treated with proton APBI. They also reported 83 percent good to excellent cosmesis as judged by providers and 93 percent by patient reports at 3 years. There were no grade 3 or higher late toxicity events, and 17 percent of patients developed grade 1 telangiectasia.[82] Another single-arm study of 76 women with median followup 12 months found 98 percent of patients reported good to excellent cosmesis with no grade 2 or higher AEs, including one transient grade 1 telangiectasia.[83]

3.3.2.4. Single-Entry Catheter Brachytherapy Versus 3DCRT

Two studies compared single-entry catheter brachytherapy with 3DCRT.[74, 80] There was no significant difference in IBR with single-entry catheter brachytherapy compared with 3DCRT at 5 years.[74, 80] Overall survival was reported by one observational study and did not show a significant difference in overall survival at 5 years.[80] There was no significant difference in total acute and late AEs.[74] There was no significant difference in tumor bed IBR, elsewhere IBR, or distant breast cancer recurrence, as shown in Table 8.

3.3.2.5. Single-Entry Catheter Brachytherapy Versus Multi-Catheter Interstitial Brachytherapy

Two observational studies compared single-entry catheter brachytherapy with multi-catheter interstitial brachytherapy with insufficient SOE.[80, 81] Single-entry catheter brachytherapy compared with multi-catheter interstitial brachytherapy was not statistically different for IBR at 5 years,[80] overall survival at 5 years,[80] cosmesis at 5 years as reported by the healthcare provider,[81] total late AEs,[81] or distant breast cancer recurrence at 5 years.

3.3.2. Results, Key Question 2: KQ 2 Results

Table 7. KQ 2. Main outcomes: comparisons of different PBI modalities

Comparison	Outcome	Timing	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
IMRT compared with 3DCRT	IBR	5 years	RR: 1.00; 95% CI: 0.36 to 2.82; I^2=N/A; RD: 0.00; 95% CI: -0.02 to 0.02 IMRT: 2.18% (7/321) vs. 3DCRT: 2.18% (7/321)	1 RCT,[72] 656 patients	No difference	Insufficient (Risk of bias, and rated down 2 levels for imprecision)
	IBR	5 years	RR: 0.25; 95% CI: 0.01 to 5.90; I^2= N/A; RD: -0.02; 95% CI: -0.08 to 0.03 IMRT: 0% (0/69) vs. 3DCRT: 2.27% (1/44)	1 observational study, [73] 104 patients	No difference	Insufficient (Risk of bias, and rated down 2 levels for imprecision)
	IBR	10 years	RR: 0.15; 95% CI: 0.01 to 3.00; I^2= N/A; RD: -0.05; 95% CI: -0.11 to 0.02 IMRT: 0% (0/60) vs. 3DCRT: 4.55% (2/44)	1 observational study,[73] 104 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	IBR	> 10 years	RR: 0.11; 95% CI: 0.01 to 1.99; I^2= N/A; RD: -0.07; 95% CI: -0.14 to 0.01 IMRT: 0% (0/60) vs. 3DCRT: 6.82% (3/44)	1 observational study,[73] 104 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Cancer-free survival	5 years	RR: 0.91; 95% CI: 0.87 to 0.95; I^2=N/A*; RD: -0.09; 95% CI: -0.13 to -0.05 IMRT: 88.11% (289/328) vs. 3DCRT: 96.95% (318/328)	1 RCT,[72] 656 patients	Favors 3DCRT	Low (Risk of bias, and rated down 1 level for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	10 years	RR: 0.05; 95% CI: 0.00 to 0.84; I^2= N/A*; RD: -0.16; 95% CI: -0.27 to -0.05 IMRT: 0% (0/60) vs. 3DCRT: 15.91% (7/44)	1 observational study,[73] 104 patients	Favors IMRT	Insufficient (Risk of bias, and rated down 1 level for imprecision)
	Cosmesis reported by patient (poor or fair)	10 years	RR: 0.06; 95% CI: 0.00 to 0.98; I^2= N/A*; RD: -0.14; 95% CI: -0.24 to -0.03 IMRT: 0% (0/60) vs. 3DCRT: 13.63% (6/44)	1 observational study,[73] 104 patients	Favors IMRT	Insufficient (Risk of bias, and rated down 1 level for imprecision)

3.3.2. Results, Key Question 2: KQ 2 Results

Comparison	Outcome	Timing	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
Multi-catheter interstitial brachytherapy compared with 3DCRT	IBR	5 years	RR: 11.00; 95% CI: 0.25 to 483.88; I^2= N/A; RD: 0.00; 95% CI: 0.00 to 0.00 Multi-catheter interstitial brachytherapy: 0% (0/3) vs. 3DCRT: 0% (0/43)	1 observational study,[80] 46 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Overall survival	5 years	RR: 0.72; 95% CI: 0.32 to 1.60; I^2= N/A; RD: -0.26; 95% CI: -0.80 to 0.28 Multi-catheter interstitial brachytherapy: 66.67% (2/3) vs. 3DCRT: 93.02% (40/43)	1 observational study,[80] 46 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 0.63; 95% CI: 0.33 to 1.20; I^2= N/A; RD: -0.11; 95% CI: -0.28 to 0.05 Multi-catheter interstitial brachytherapy: 18.82% (16/85) vs. 3DCRT: 30% (12/40)	1 RCT,[66-70] 125 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	10 years	RR: 0.56; 95% CI: 0.27 to 1.13; I^2= N/A; RD: -0.12; 95% CI: -0.28 to 0.04 Multi-catheter interstitial brachytherapy: 15.29% (13/85) vs. 3DCRT: 27.5% (11/40)	1 RCT,[66-70] 125 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	> 10 years	RR: 0.64; 95% CI: 0.32 to 1.27; I^2= N/A; RD: -0.10; 95% CI: -0.26 to 0.06 Multi-catheter interstitial brachytherapy: 17.65% (15/85) vs. 3DCRT: 27.5% (11/40)	1 RCT,[66-70] 125 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)

3.3.2. Results, Key Question 2: KQ 2 Results

Comparison	Outcome	Timing	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
Proton compared with 3DCRT	IBR	10 years	RR: 2.77; 95% CI: 0.50 to 15.44; I^2= N/A; RD: 0.07; 95% CI: -0.08 to 0.21 Proton: 10.53% (2/19) vs. 3DCRT: 3.80% (3/79)	1 observational study,[79] 98 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 4.85; 95% CI: 1.84 to 12.78; I^2= N/A*; RD: 0.29; 95% CI: 0.07 to 0.52 Proton: 36.84% (7/19) vs. 3DCRT: 7.59% (6/79)	1 observational study,[79] 98 patients	Favors 3DCRT	Insufficient (Risk of bias, and rated down 1 level for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	10 years	RR: 6.93; 95% CI: 1.81 to 26.49; I^2= N/A*; RD: 0.23; 95% CI: 0.02 to 0.43 Proton: 26.32% (5/19) vs. 3DCRT: 3.80% (3/79)	1 observational study,[79] 98 patients	Favors 3DCRT	Insufficient (Risk of bias, and rated down 1 level for imprecision)
	Cosmesis reported by patient (poor or fair)	5 years	RR: 2.08; 95% CI: 0.41 to 10.52; I^2= N/A; RD: 0.05; 95% CI: -0.09 to 0.20 Proton: 10.53% (2/19) vs. 3DCRT: 5.06% (4/79)	1 observational study,[79] 98 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Cosmesis reported by patient (poor or fair)	10 years	RR: 2.08; 95% CI: 0.20 to 21.75; I^2= N/A; RD: 0.03; 95% CI: -0.08 to 0.13 Proton: 5.26% (1/19) vs. 3DC RT: 2.53% (2/79)	1 observational study,[79] 98 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
Single-entry catheter brachytherapy compared with 3DCRT	IBR	5 years	RR: 1.12; 95% CI: 0.00 to +∞; I^2= 0%; RD: 0.01; 95% CI: -0.20 to 0.22 Single-entry catheter brachytherapy: 2.62% (8/305) vs. 3DCRT: 1.39% (1/72)	2 observational studies,[74, 80] 377 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Overall survival	5 years	RR: 1.03; 95% CI: 0.94 to 1.14; I^2= N/A; RD: 0.03; 95% CI: -0.06 to 0.12 Single-entry catheter brachytherapy: 96.23% (51/53) vs. 3DCRT: 93.02% (40/43)	1 observational study,[80] 96 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 1.63; 95% CI: 0.72 to 3.72; I^2= N/A; RD: 0.11; 95% CI: -0.04 to 0.26 Single-entry catheter brachytherapy: 28.17% (71/252) vs. 3DCRT: 17.24% (5/29)	1 observational study,[74] 281 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)

3.3.2. Results, Key Question 2: KQ 2 Results

Comparison	Outcome	Timing	Findings	Study Design and Sample Size	Direction of Effect	Strength of Evidence
Single-entry catheter brachytherapy compared with multi-catheter interstitial brachytherapy	IBR	5 years	RR: 0.22; 95% CI: 0.01 to 4.62; I^2= N/A; RD: 0.02; 95% CI: -0.02 to 0.06 Single-entry catheter brachytherapy: 1.89% (1/53) vs. Multi-catheter interstitial brachytherapy: 0% (0/3)	1 observational study,[80] 56 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Overall survival	5 years	RR: 1.44; 95% CI: 0.65 to 3.22; I^2= N/A; RD: 0.30; 95% CI: -0.24 to 0.83 Single-entry catheter brachytherapy: 96.23% (51/53) vs. multi-catheter interstitial brachytherapy: 66.67% (2/3)	1 observational study,[80] 56 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)
	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 0.67; 95% CI: 0.15 to 2.96; I^2= N/A; RD: -0.04; 95% CI: -0.15 to 0.08 Single-entry catheter brachytherapy: 7.14% (2/28) vs. Multi-catheter interstitial brachytherapy: 10.67% (8/75)	1 observational study,[81] 103 patients	No difference	Insufficient (Risk of bias, and rated down 3 levels for imprecision)

Abbreviations: ∞ = infinity; 3DCRT = 3-dimensional conformal external beam radiotherapy; CI = confidence interval; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; KQ = Key Question; N/A = not applicable; PBI = partial breast irradiation; RCT = randomized clinical trial; RD = risk difference; RR = relative risk

* Results are statistically significant at two tailed $p<0.05$.

Table 8. KQ 2. Secondary outcomes

Comparison	Outcome	Timing	Findings	Direction of Effect	Study Design and Sample Size
IMRT compared with 3DCRT	Total AE	Acute	IRR: 0.54; 95% CI: 0.38 to 0.77; I^2= N/A* IMRT: 90% (54/60) vs. 3DCRT: 165.91% (73/44)	Favors IMRT	1 observational study,[73] 104 patients
	Total AE	Late	IRR: 0.46; 95% CI: 0.28 to 0.77; I^2= N/A* IMRT: 40% (24/60) vs. 3DCRT: 86.36% (38/44)	Favors IMRT	1 observational study,[73] 104 patients
Multi-catheter interstitial brachytherapy compared with 3DCRT	Total AE	Late	IRR: 1.18; 95% CI: 0.79 to 1.77; I^2= N/A Multi-catheter interstitial brachytherapy: 97.70% (85/87) vs. 3DCRT: 82.5% (33/40)	No difference	1 RCT, [70 66-69] 127 patients
	Distant breast cancer recurrence	5 years	RR: 11.00; 95% CI: 0.25 to +∞; I^2= N/A; RD: 0.00; 95% CI: 0.00 to 0.00 Multi-catheter interstitial brachytherapy: 0% (0/3) vs. 3DCRT: 0% (0/43)	No difference	1 observational study,[80] 46 patients

3.3.2. Results, Key Question 2: KQ 2 Results

Comparison	Outcome	Timing	Findings	Direction of Effect	Study Design and Sample Size
Proton compared with 3DCRT	Total AE	Late	IRR: 3.95; 95% CI: 2.11 to 7.40; I^2= N/A* Proton: 100% (19/19) vs. 3DCRT: 25.32% (20/79)	Favors 3DCRT	1 observational study,[79] 98 patients
	Elsewhere IBR	10 years	RR: 2.77; 95% CI: 0.50 to 15.44; I^2= N/A; RD: 0.07; 95% CI: -0.08 to 0.21 Proton: 10.53% (2/19) vs. 3DCRT: 3/79)	No difference	1 observational study,[79] 98 patients
Single-entry catheter brachytherapy compared with 3DCRT	Total AE	Acute	IRR: 1.02; 95% CI: 0.61 to 1,71; I^2= N/A* Single-entry catheter brachytherapy: 56.35% (142/252) vs. 3DCRT: 55.17% (16/29)	No difference	1 observational study,[74] 281 patients
	Total AE	Late	IRR: 1.29; 95% CI: 1.00 to 1.66; I^2= N/A Single-entry catheter brachytherapy: 293.25% (739/252) vs. 3DCRT: 227.59% (66/29)	No difference	1 observational study,[74] 281 patients
	AE grade ≥ 2	Acute	IRR: 1.34; 95% CI: 0.41 to 4.37; I^2= N/A* Single-entry catheter brachytherapy: 13.89% (35/252) vs. 3DCRT: 10.34% (3/29)	No difference	1 observational study,[74] 281 patients
	AE grade ≥ 2	Late	IRR: 1.48; 95% CI: 0.69 to 3.19; I^2= N/A Single-entry catheter brachytherapy: 35.71% (90/252) vs. 3DCRT: 24.14% (7/29)	No difference	1 observational study,[74] 281 patients
	Tumor bed IBR	5 years	RR: 1.30; 95% CI: 0.07 to 23.01; I^2= N/A; RD: 0.02; 95% CI: 0.00 to 0.04 Single-entry catheter brachytherapy: 1.98% (5/252) vs. 3DCRT: 0% (0/29)	No difference	1 observational study,[74] 281 patients
	Elsewhere IBR	5 years	RR: 0.23; 95% CI: 0.02 to 2.46; I^2= N/A; RD: -0.03; 95% CI: -0.09 to 0.04 Single-entry catheter brachytherapy: 0.79% (2/252) vs. 3DCRT: 3.45% (1/29)	No difference	1 observational study,[74] 281 patients
	Distant breast cancer recurrence	5 years	RR: 0.81; 95% CI: 0.02 to 40.24; I^2= N/A; RD: 0.00; 95% CI: 0.00 to 0.00 Single-entry catheter brachytherapy: 0% (0/53) vs. 3DCRT: 0% (0/43)	No difference	1 observational study,[80] 96 patients

3.3.2. Results, Key Question 2: KQ 2 Results

Comparison	Outcome	Timing	Findings	Direction of Effect	Study Design and Sample Size
Single-entry catheter brachytherapy compared with multi-catheter interstitial brachytherapy	Total AE	Late	IRR: 0.91; 95% CI: 0.53 to 1.58; I^2= N/A Single-entry catheter brachytherapy: 60.71% (17/28) vs. Multi-catheter interstitial brachytherapy: 66.67% (50/75)	No difference	1 observational study,[81] 103 patients
	Distant breast cancer recurrence	5 years	RR: 0.07; 95% CI: 0.00 to 3.27; I^2= N/A; RD: 0.00; 95% CI: 0.00 to 0.00 Single-entry catheter brachytherapy: 0% (0/53) vs. Multi-catheter interstitial brachytherapy: 0% (0/3)	No difference	1 observational study,[80] 56 patients

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiotherapy; AE = adverse event; CI = confidence interval; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IRR = incidence rate ratio; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RD = risk difference; RR = relative risk

* Results are statistically significant at two tailed $p<0.05$.

3.4. Contextual Question

3.4.1. Summary

We did not identify any studies that explicitly addressed the construct of financial toxicity, defined as subjective or objective financial distress and hardship experienced by patients due to cancer-related (or anticipated) treatment. However, we identified studies that addressed various closely related concepts, such as direct nonhealthcare costs (e.g., transportation to receive care) and indirect costs (e.g., loss of productivity). A total of eight studies[55, 58, 75, 82, 86-89] were included for the CQ, including three RCTs,[55, 58, 87] three comparative observational studies,[75, 86, 88] one single-arm observational study,[82] and one cost evaluation study.[89] Two studies were conducted in the United States, five in Europe, and one in India. The PBI modalities evaluated were IORT (n=2), multi-catheter interstitial brachytherapy (n=3), IMRT (n=2), 3DCRT (n=2), single-entry catheter brachytherapy (n=1), and proton radiation therapy (n=1). Four studies evaluated time away from work, transportation to receive care, and related costs in monetary value. Four studies reported subjective "financial difficulties" using the EORTC QLQ-C30 questionnaire. The literature suggested that PBI was associated with lower transportation costs and days away from work compared with WBI. PBI was also associated with less subjective financial difficulties at various time points after radiotherapy.

3.4.2. Detailed Findings

Four studies (1 RCT, 1 comparative observational study, 1 single-arm observational study, and 1 cost evaluation study) evaluated patients' direct nonmedical cost, time away from work, transportation to receive care and related costs in monetary value.

In a subset study of the TARGIT-A trial,[87] 485 UK patients received IORT APBI (20 Gy in one fraction) (n=249) or WBI in 15 fractions(n=236). The IORT group reported significantly shorter total distance driven for planning, consent, and receiving radiotherapy than the WBI group (mean: 87.1 miles [standard error 19.1] vs. 392.3 miles [standard error 30.2], p<0.001). The mean total travel time for radiotherapy was 3.0 hours (standard error 0.53) for IORT and 14.0 hours (standard error 0.92) for WBI (p<0.0001).

A comparative observational study[86] conducted in France evaluated 96 women who received 3DCRT APBI (40 or 42 Gy in 10 fractions over 5 days, n=48) or WBI (50 Gy in 25 fractions to the whole breast with optional boost of 16 Gy for 5 to 6.5 weeks, n=48) between 2007 and 2012. Although patients in the 3DCRT APBI group travelled significantly longer distances from home to hospital than those in the WBI group (35 kilometers [standard deviation (SD): 43 kilometers] vs. 10 kilometers [SD: 8 kilometers]), respectively; P <0.001), the total transportation costs were not statistically higher in the 3DCRT APBI group (€553 [SD: 1240] vs. €532 [SD: 568], p=0.07) due to reduction of required hospital visits. The 3DCRT APBI group reported significantly less sick leave (2% vs. 23%, respectively) than the WBI group and fewer sick days (10 days vs. 43 days). Thus, the costs of sick leaves were significantly lower in the 3DCRT APBI group (€13 [SD 93] per patient vs. €539 [SD 1016] per patient, p=0.002).

In a U.S. single-arm observational study,[82] 100 patients received proton APBI (34 Gy in 10 fractions, twice daily) between 2010 and 2019. On average, patients spent 5 days (interquartile range [IQR]: 2-5 days) away from work and 10 hours (SD: 4.3 hours) in clinic to receive radiation treatment. The median out-of-pocket cost was $700 (IQR: $100-$1,600).

3.4. Results, Contextual Question

A U.S. cost evaluation analysis[89] compared direct nonmedical patient cost between APBI modalities (single-entry catheter brachytherapy (34 Gy in 10 twice-daily fractions), multi-catheter interstitial brachytherapy (34 Gy in 10 twice-daily fractions), 3DCRT (38.5 Gy in 10 twice-daily fractions), IMRT (38.5 Gy in 10 twice-daily fraction) and WBI (50 Gy in 25 fractions) based on the 2003 Medicare Fee Schedule. The direct nonmedical costs included time and transportation costs related to radiotherapy. The study found that the direct nonmedical patient costs of APBI were $500 with no difference between different APBI modalities; direct nonmedical patient costs of WBI were $1,100.

Four studies (2 RCTs and 2 comparative observational studies)[55, 58, 75, 88] adopted the EORTC QLQ-C30's "financial difficulties" question. The question used a 4-point Likert scale from 1 (not at all) to 4 (very much) to measure subjective financial distress related to radiation therapy.

The Florence trial, conducted in Italy, compared APBI using IMRT (30 Gy in 5 fractions, every 2 days) to WBI (50 Gy in 25 fractions, once daily followed by a boost to the tumour bed of 10 Gy in 5 fractions).[58] At 2-year followup, patients who received APBI reported significantly less financial difficulties than those who received WBI; but the difference was not significantly difference immediately after radiation.

The GEC-ESTRO trial,[55] conducted in seven European countries, compared APBI based on multi-catheter interstitial brachytherapy (32 Gy in 8 fractions or 30.3 Gy in 7 fractions given twice daily, or pulsed-dose-rate brachytherapy to a total dose of 50 Gy within 4-5 days) to WBI (50 Gy in 25-28 fractions, once daily, for 6-7 weeks + 10 Gy boost in 5 fractions). The multi-catheter interstitial brachytherapy group reported significant less financial stress immediately after radiation and at 3 months. But the difference was not significant at 5-year followup.

Another comparative observational study evaluated 48 Indian women with early breast cancer who received APBI using multi-catheter interstitial brachytherapy (34 Gy in 10 fractions, 2 fractions per day for 5–7 days, n=23) or WBI (45 Gy in 25 fractions plus tumor bed boost either with electrons (15 Gy in 6 fractions, n=22) or interstitial implant (10 Gy in 1 fraction, n=3).[88] At a median followup of 3 years, patients with multi-catheter interstitial brachytherapy reported less financial difficulty than those received WBI, but the difference was not statistically significant.

In a comparative observational study conducted in the Netherlands,[75] APBI using the IORT technique (23.3 Gy in one fraction) was found to be associated with significantly less financial difficulties immediately after radiation therapy, compared with APBI using IMRT or 3DCRT (3.85 Gy in 10 fractions, once daily for a total of 38.5 Gy). However, the difference was not significant at 3 months or 1 year.

4. Discussion

4.1. Overview

We conducted a systematic review to assess the comparative effectiveness of partial breast irradiation (PBI) and whole breast irradiation (WBI) for early-stage breast cancer. We assessed ipsilateral breast recurrent (IBR), cancer-free survival, overall survival, cosmesis, adverse events (AEs), and other outcomes. We also assessed these outcomes in relation to patient and tumor characteristics, as well as treatment parameters such as modality, dose, and fractionation.

High strength of evidence (SOE) showed that IBR was not statistically different between PBI and WBI at 5-year and 10-year followup. PBI and WBI were not statistically different in terms of the risk of IBR in the tumor bed or elsewhere in the breast. These findings suggest that WBI is not superior to PBI in preventing IBR among patients who are similar to those who enrolled in the clinical trials included in this analysis. On subgroup analysis, one study showed better IBR at 10 years with PBI in patients with smaller tumor size (<1 cm) in comparison to larger tumors.[21] There were otherwise no apparent differences in IBR or other outcomes according to patient, tumor, and treatment characteristics, although the data for individual subgroups were insufficient to draw conclusions and require further study. We found no statistical differences in cancer-free survival or overall survival between PBI and WBI.

PBI was associated with significantly lower rate of acute AEs in comparison to WBI. There was insufficient evidence to draw comparative conclusions regarding cosmetic outcomes in the aggregate analysis. On subgroup analysis according to treatment schedule, there was a significantly higher rate of patient- and provider-rated adverse cosmetic outcome, as well as a higher rate of acute AEs among patients who received twice-daily treatment for 10 days using external beam radiotherapy compared with treatment once every 2 days for 5 fractions. Additional data are needed to further evaluate this finding. Comparisons between modalities were largely limited by insufficient SOE.

Intraoperative radiotherapy (IORT) was evaluated separately from other PBI modalities due to a markedly different treatment planning approach, dose, and method of treatment delivery. In two randomized clinical trials (RCTs) involving 4,756 patients, IBR was significantly higher with IORT compared with WBI at 5-, 10-, and >10-year followup, in contrast to the similar IBR rate observed with other PBI modalities. There were no differences in overall survival, cancer-free survival, or other outcomes. IORT was associated with a significantly lower rate of acute AEs in comparison to WBI, as well as lower late grade ≥2 AEs.

Studies of PBI consistently demonstrate lower transportation costs, fewer days away from work, and less subjective financial difficulties in comparison to standard fractionation WBI.

4.2. Findings in Relation to What Is Known

The literature on PBI has proliferated substantially in recent years. However, evidence remains limited about the influence of moderate risk factors in selecting patients most appropriate for PBI treatment, or determining the optimal treatment target volume, radiation dose, fractionation, and modality. Current guidelines recommend PBI as a treatment with similar results to WBI for selected patients.[26, 90-92] The findings of our systematic review and meta-analyses align with these guidelines and are consistent with results from two recent systematic reviews.[34, 93]

4. Discussion

In the era of breast conserving therapy with WBI, IBR was found to be associated with increased risk of distant metastasis[94] and reduced overall survival.[95] In-breast recurrences have been implicated as sources of potential future distant metastases. Therefore, given that we found no difference in IBR between PBI and WBI, it is consistent that we also observed no differences in cancer-free survival or overall survival. Additionally, because WBI exposes more tissue to radiation and can be associated with higher doses to organs at risk, including both the heart and lung, evaluation of overall survival is critically important to evaluate possible effects of treatment-related toxicity outcomes. No statistical differences were identified between overall survival comparing WBI or PBI.

We found that PBI was associated with significantly less acute toxicity compared with WBI. This finding likely reflects the consequences of a smaller amount of irradiated tissue and generally a shorter course of therapy to a lower cumulative dose. In a detailed examination, grade 1 events were not statistically different; however, grade 2 and 3 events were significantly lower. Grade 3 acute toxicity events were very few, but numerically lower for PBI, largely as a result of the differences reported in the GEC-ESTRO study. Just three studies with significant heterogeneity reported on grade 3 events, with wide confidence intervals. The broad applicability of toxicity rates from the GEC-ESTRO study is limited because of the use of the multi-catheter technique, which represents a rarely used treatment option in the United States.[96] Nevertheless, the lack of increased toxicity particularly considering the interventional and technical nature of this modality is noteworthy. Multi-catheter interstitial brachytherapy and IORT were associated with lower rates of acute toxicity compared with WBI. Among studies comparing external beam PBI (intensity-modulated radiation therapy [IMRT] or 3-dimensional conformal external beam radiation therapy [3DCRT]) to WBI, there were heterogenous results with some describing no statistical differences in acute toxicity,[22, 24, 40, 51-53, 58-61, 64, 65] and others reporting reduced acute toxicity with PBI[22]. In the very limited data with direct comparison between PBI modalities, both IMRT and single-entry brachytherapy appeared to be associated with lower rates of acute toxicity than 3DCRT. IMRT is associated with improved dose homogeneity, and brachytherapy reduces the volume of breast irradiation, both of which may be associated with reduced acute toxicity.

In review of long-term toxicity, there was no statistical difference between PBI and WBI. With smaller treatment volumes and statistically lower rates of acute AEs, the lack of statistical difference in long-term toxicity is worthy of further exploration. Late AEs in breast cancer patients develop in response to a variety of factors, many of which are relevant to these comparisons, such as normal tissue repair/response to radiation, target volume, dose heterogeneity, and proximity to normal tissues, such as skin or chest wall. Importantly, there is no clear relationship between the risk for acute AEs and the delayed AEs in patients with breast cancer[97], with some data suggesting that lower risk for acute events does not always translate to lower risk for delayed events. We observed this finding, with lower risk for acute toxicity with PBI, but no difference with late AEs. Delayed events, such as fibrosis, breast lymphedema, telangiectasia, and fat necrosis are mediated by different, but related pathways.[98] These events may also be more sensitive to dose and fractionation, as well as normal tissue recovery, such as sub-lethal damage repair pathways. Similarly, the risks for developing late AEs from breast radiotherapy of any kind may be reduced over the last two decades through technological improvements in the target definition, localization, and dose distributions. Improved dose distributions in breast radiotherapy have showed lower rates of AEs,[99] and this has been observed in comparisons of PBI with 3DCRT and IMRT. [73] This highlights the challenge of

evaluating outcomes over time among treatments with evolving technology. For example, while some institutional reports of early accelerated partial breast irradiation (APBI) experiences reported high rates of cosmetic deterioration, in the most recent published RCTs, the risks for both cosmetic change and AEs were lower with ABPI.[23, 55-57] Similarly, early experiences with PBI using passive scatter proton therapy report high rates of late skin toxicities, which have not been observed in more recent studies with updated treatment and planning techniques. For example, telangiectasia of any grade is reported in as many as 69 percent of patients treated with passive scatter proton therapy, in contrast to as few as 1.3 percent with pencil beam scanning.[79, 83 84, 85]

The lack of significant difference in cancer-free survival and overall survival between PBI and WBI is consistent with other systematic reviews.[34, 93] One meta-analysis reported a decrease in nonbreast cancer mortality with PBI compared with WBI;[100] however, there are methodological concerns regarding the selection of studies and reported results.[101] While the TARGIT-A trial reported reduced nonbreast cancer deaths favoring IORT compared with WBI, this observation is inconsistent with expectations for the timeline to development of AEs and unsupported by other evidence examining IORT, as well as numerous other studies of PBI that also had excellent cardiac sparing.

4.3. Clinical Implications and Applicability of Findings

Appropriate patient selection is a critically important aspect of the success of PBI. There is broad consensus in multiple treatment guidelines and systematic reviews that PBI is an acceptable treatment option for patients with clinical and tumor characteristics similar to those represented on clinical trials, for example, postmenopausal age range, estrogen receptor (ER) positive status, grade 1-2, no lymph node involvement, and tumor size ≤2 cm. The results presented in this report represent data from 15,276 patients who participated in RCTs of PBI versus WBI, more than three-fold the number of patients who participated in clinical trials that led to the adoption of breast conserving surgery and WBI as a standard treatment approach.[20] In aggregate, the results of our meta-analysis and systematic review showed no difference between PBI and WBI for selected patients. The finding of reduced acute toxicity with PBI represents a significant finding that will meaningfully inform patient and physician decision making.

Uncertainty remains regarding the magnitude of increased risk associated with features that are perceived as less favorable that were included within the eligibility criteria but represent a minority of patients who participated, for example age <50 years, invasive lobular carcinoma, tumor size 2.1-3 cm, grade 3, ER negative status, Human Epidermal Growth Factor Receptor 2 (HER2) positive status, positive for lymphovascular invasion, or elevated Ki-67. Our analysis revealed the lack of data on the outcomes in these subgroups and highlight the importance of future investigation to develop more robust evidence to inform treatment recommendations.

4.3.1. Size

Eligibility criteria for clinical trials of PBI typically included patients with tumor size up to 3 cm. Subgroup analysis from NSABP B-39/RTOG 0413 showed that APBI was less favorable in patients with larger tumor size.[21] Similar findings were observed in the American Society of Breast Surgeons MammoSite Registry trial, with larger tumor size (as a continuous variable) associated with significantly higher rate of IBR.[102] These observations suggest that tumor size may be a consideration in selecting patients for APBI. While APBI may be considered an acceptable option for tumors that are larger (e.g. 1.5-3 cm), clinicians may consider adjusting the

treatment approach with a dose and fractionation that allows for treatment of a greater proportion of the breast volume with mini-tangents that more closely approximate a whole-breast treatment field, such as the technique for PBI used on the IMPORT LOW study.[25, 54] Co-existence of large tumor size with other moderate risk factors may influence decisions regarding the suitability of PBI.

4.3.2. Age

The age of 40-50 years has previously been considered as a cautionary clinical feature for patient selection for PBI.[26, 27] Our analysis did not show a difference in IBR or other outcomes according to age or menopausal status. Representation of patients aged 40-49 years on the included RCTs ranged from no patients[25, 54] to 38 percent of the enrolled population.[21] For example, NSABP B39 exerted a deliberate effort to increase enrollment in the younger age range and included 1,621 women aged <50 years. In subgroup analysis according to menopausal status (a close approximation of age <50 years with 1,588 premenopausal patients), there was no statistically significant difference in IBR. Relative to the information available when clinical guidelines were previously drafted, these findings represent a meaningful increase in the amount of data available to inform clinical decisions about PBI according to age and menopausal status, notwithstanding the lack of statistical power to definitively conclude whether age <50 years represents an adverse risk factor for IBR.

4.3.3. Hormone Receptor Status, Grade, and Nodal Status

Analogous findings were observed for hormone receptor status, grade, and nodal status. Among 966 patients with ER negative tumors enrolled in three clinical trials,[21, 22, 52, 53 24, 58-61] there was no apparent difference in IBR according to ER status. While ER expression is well established for systemic therapy decision making, its role as a selection criterion for PBI remains a topic of discussion. There is discrepancy between European Society for Radiotherapy and (ESTRO) guidelines, which include ER negative tumors as suitable for PBI,[27] and American Society for Radiation Oncology (ASTRO) guidelines, which do not.[26]

Similarly, there was no difference in IBR according to lymph node status (424 patients[21]) or tumor grade (235 patients with grade 3 tumor). Previous studies have demonstrated an increased risk of IBR with PBI among patients with tumors that are ER negative,[102-105] grade 3,[103] or with involved lymph nodes.[105] Due to the limited sample size and low number of events in each of the subgroups evaluated, there is insufficient evidence in the current analysis to determine the magnitude of increased risk of IBR associated with each potential adverse risk factor.

4.3.4. Margins

While each of the included studies required negative margins to be considered eligible for PBI, there was variability in the width of required margin. Many studies required a margin of at least 2 mm or greater.[23-25, 40, 54-61, 64, 65, 70 66-69] In the two largest studies comprising 6,351 patients,[22, 52, 53] a “microscopically clear” margin of no tumor on ink was required. This definition of a negative margin is consistent with current guidelines for invasive breast cancer treated with breast conserving surgery[106] and whole breast radiation and raises the question of whether a wider margin is required for patients undergoing PBI.

4.3.5. Ductal Carcinoma In Situ

Patients with ductal carcinoma in situ (DCIS) were included in three clinical trials comprising a total of 1,372 patients;[21-23, 52, 53, 55-57] many RCTs specifically excluded patients with DCIS.[24, 25, 37, 40, 54, 58-61, 64, 67 51] Tumor characteristics of patients with DCIS who were included are not reported, such as the proportion with high grade DCIS and the size of the lesion; this information would be helpful for the authors of the included studies to make available. Previous guidelines specified that patients with DCIS with favorable risk features that are consistent with the inclusion criteria for studies evaluating omission of adjuvant radiotherapy were considered either suitable for PBI,[26] or in an intermediate risk category.[27] The American Society of Breast Surgeons MammoSite Registry trial observed excellent outcomes among 300 women with DCIS.[107] Among 22 patients with DCIS treated with APBI using IMRT on the Florence clinical trial, there were no recurrences or late toxicity with median 9.2-year followup.[108] The results of our analysis represent an updated summary that did not observe a significant difference in the rate of IBR among patients with DCIS treated with PBI compared with WBI. These findings suggest that, within the limitations of subgroup analysis, PBI is not worse than WBI in this subgroup, but we are not able to inform which patients with DCIS may or may not be favorable candidates for PBI. Among patients with "good-risk DCIS" (mammographically detected, <2.5 cm, low or intermediate grade), results from the RTOG 9804 clinical trial support the option of considering omission of radiotherapy.[109]

4.3.6. Cosmetic Outcomes

We observed a significantly higher rate of patient- and provider-rated poor or fair cosmesis among patients treated with twice-daily fractionation for 10 fractions with external beam radiotherapy compared with once every 2 days for 5 fractions, as well as a higher rate of acute AEs. For PBI, it has been suggested that twice-daily treatment might not allow adequate time for repair of sublethal cellular damage, which may influence the incidence of AEs and the cosmetic outcome.[110] Additionally, the prescription dose for PBI using the most common dose and fractionation, 38.5 Gy in 10 fractions, represents a higher biologically equivalent dose than the WBI regimen,[110] and in combination with twice-daily fractionation represents an intensive treatment. In one large study, the investigators concluded that "it is difficult to recommend the twice per day regimen,"[22, 52, 53] which is consistent with ESTRO consensus guidelines that recommend against use of this regimen.[111] However, we note that our findings do not include data from the largest clinical trial of APBI using twice daily fractionation, NSABP B-39, which has not yet published cosmetic outcome results.

Three clinical trials of PBI showed an improved cosmetic outcome with PBI compared to WBI. In the IMPORT LOW clinical trial, 21 percent of the overall cohort reported breast appearance change, with significantly lower rates in the partial breast group.[54] Due to differences in the scale used for assessment, these results were not able to be combined in the aggregate analysis of cosmesis. Another study with APBI delivered every other day in 5 fractions demonstrated improved patient and physician reported cosmetic outcome.[24] A third study found improved cosmesis for PBI delivered as either multicatheter interstitial brachytherapy or electron beam PBI in 25 fractions.[68] These observations of more favorable cosmetic outcomes with different dose and fractionation contrast with the finding of inferior cosmesis associated with APBI on the RAPID study [22, 52, 53], and highlight the influence of dose, fractionation, and treatment technique on the cosmetic outcome.

We found that most of the included studies required portal imaging for treatment setup verification, which was routine practice at the time the clinical trials were designed but is not reflective of current practice, with widespread use of daily imaging, similar to the approach described by Franceschini et al.[40] Additionally, most of the randomized trials included in our analysis used a 1 cm expansion to create the planning target volume (PTV), which is larger than contemporary practice when daily image guidance is used. The treatment planning approach most commonly used in the largest RCTs of PBI—with twice-daily fractionation, lack of daily imaging, and treating a large target volume—all may cumulatively influence the cosmetic outcome. Our results lend support to ongoing efforts to define a more optimal treatment approach, including defining the treatment target,[40] use of daily image guidance, and evaluating the outcomes of regimens for once-daily treatment regimens[10, 83]. In light of data demonstrating a relationship between cosmetic outcome and the proportion of breast receiving high-dose radiotherapy (such as the proportion of breast receiving 50% and 100% of the prescribed dose)[112-115] efforts to define optimal treatment planning constraints are also needed. However, for PBI using dose regimens similar to WBI, the volume of irradiated breast is likely not a limiting consideration, and larger treatment volumes may be acceptable. For example, guidelines from the Royal College of Radiologists are supportive of 26 Gy in 5 fractions for PBI, a dose that was well tolerated WBI on the FAST-Forward clinical trial.[10] ESTRO observed support for 26 Gy in 5 fractions but did not reach the voting threshold to endorse it as a consensus[111].

4.3.7. Adverse Events

The rates of acute AEs with PBI were lower than WBI. However, it is important to note that the WBI treatment for many of the studies used conventional fractionation with 2 Gy daily fractions over 5 weeks, often with a boost. The use of a tumor bed boost is associated with lower risk for IBR for some women with breast cancer; however, it is also associated with an increased risk for AEs, including late AEs with fibrosis. Conventionally fractionated WBI has largely been supplanted by hypofractionation completed over approximately 3 weeks, which is associated with lower risk for AEs.[8] Following publication of the UK FAST-Forward study, a shorter course of "ultrahypofractionated" WBI completed in 5 fractions is increasingly used in clinical practice and has been associated with mild acute toxicity that may be slightly reduced in comparison to hypofractionated regimens.[116] This highlights the challenge of interpreting the applicability of the finding of reduced acute AEs with PBI to modern breast radiotherapy treatment.

As acute AEs from breast radiotherapy typically resolve shortly after radiotherapy, late AEs are perhaps more relevant to clinical applicability. In the aggregate analysis, we did not observe a difference in late AEs between PBI and WBI, largely due to significant inconsistency between studies. For example, the RAPID study reported significantly increased late toxicity with APBI compared to WBI.[22] In contrast, several studies, including IMPORT LOW and GEC-ESTRO, have reported reduced late AEs with PBI compared to WBI.[40, 51, 54, 56] This heterogeneity is likely attributable to various PBI dose and fractionation regimens between studies.

4.3.8. Intraoperative Radiotherapy

Long-term followup of the ELIOT trial reported that the risk of IBR was higher with IORT than WBI,[62, 63] even among patients classified as being "suitable" for PBI according to ASTRO guidelines.[62] In a "very low risk" group defined by tumor size <1 cm, grade 1, Luminal A, and Ki-67 <14 percent, the 15-year rate of IBR was 8.1 percent with IORT and 3.1 percent with

WBI, which was not a statistically significant difference, leading the authors to advocate that selection criteria for IORT should be more strict than the suitable category according to ASTRO guidelines. Concerns have been raised that the high rate of IBR with IORT on the ELIOT trial may be partially attributable to suboptimal treatment technique, such as selection tube diameter and electron energy.[117] In a retrospective review of the Verona University Hospital experience with 7.1 year median follow-up, the rate of true local recurrence with IORT with electrons was reported as 2 percent.[118] Another retrospective study with 3-year median follow-up of IORT with electrons reported 1.6 percent cumulative incidence of IBR among patients considered suitable by ASTRO criteria.[119] Guidelines for IORT with electrons from the ESTRO IORT Task Force recommend selection of patients with tumors ≤2 cm, grade 1/2, and Luminal A;[120] these recommendations were issued prior to publication of long-term follow-up from the ELIOT study.[62]

The TARGIT-A clinical trial was designed to allow patients to receive IORT either intraoperatively before pathology was available (the prepathology stratum) or separately as a delayed procedure (postpathology stratum). We note that the authors of the TARGIT-A clinical trial reported that the rate of IBR was noninferior in the stratum of patients treated with IORT during lumpectomy compared with WBI;[44] concerns have been expressed regarding the statistical analysis and the focus on only the immediate IORT cohort rather than the intention-to-treat population.[121, 122] Results from our aggregate analysis of the available data suggests that caution is still warranted[123] regarding a higher risk of IBR even with IORT delivered intraoperatively at the time of lumpectomy.

With improved patient selection and more optimal treatment technique, the question remains regarding whether IORT could potentially be associated with a lower rate of recurrence than we observed.

Distinction may be made between IORT using 50 kV photons with the Intrabeam device, with complete 5-year follow-up reported in the TARGIT-IORT studies,[43, 44] and IORT using electrons, with 12.4 year follow-up in the ELIOT study.[62] The treatment technique and physical properties of the two different IORT methods are markedly different and may be considered as separate treatment modalities, as has been described in guidelines from both ASTRO[26] and ESTRO.[120]

We observed fewer acute AEs and late AEs grade ≥2 with IORT compared to WBI. Studies that evaluated quality of life measures found improved breast-related quality of life outcomes,[50] less breast and arm symptoms, and fewer functional limitations with IORT than with WBI.[124] There are differing data on whether IORT reduces the incidence of breast pain compared to WBI,[124, 125] and similarly mixed findings regarding cosmetic outcome. Analysis of photographs from 342 patients enrolled on the TARGIT trial reported a higher rate of favorable cosmetic outcome with TARGIT compared to WBI.[126] Among 126 patients who were treated on the post-pathology cohort of the TARGIT trial, patient-reported cosmetic outcomes were similar between IORT and WBI.[50] In one study that compared quality of life measures between electron IORT and external beam PBI, there were no clinically relevant differences in quality of life according to treatment technique.[77]

Perhaps the most attractive aspect of IORT is the shortest overall treatment time of any radiotherapy modality, with the possibility of completing radiotherapy simultaneously with breast surgery. Patients may understandably favor the convenience of IORT.[127, 128] Completion of IORT during the same anesthesia episode as breast surgery appears to have a lower rate of IBR than when it is completed at a later time as a separate procedure, as observed in the

TARGIT-A trial.[43, 44] IORT is reported to result in significantly less travel time and patient cost than adjuvant breast radiotherapy approaches,[87] which may be particularly meaningful in enhancing access to breast conserving therapy in resource-limited countries.[129] IORT has also been advocated as an efficient method of breast radiotherapy among older women who have a low risk of recurrence and may consider omitting radiotherapy altogether, as is currently being evaluated on the TARGIT-E study.[130]

Our findings present an updated analysis that shows a significantly higher rate of IBR with IORT at 5-, 10-, and >10-year followup compared with WBI. These results contrast with findings from our analysis of PBI using other treatment modalities (3DCRT, IMRT, multi-catheter interstitial brachytherapy). Among highly selected, low-risk patients, it is plausible that some may acknowledge the higher risk of IBR yet place greater value on the efficiency, low financial impact, and minimal toxicity of IORT.[127, 128, 131]

4.3.9. Single-Entry Catheter Brachytherapy

SOE supporting PBI using single-entry catheter brachytherapy is insufficient to draw conclusions. Uncontrolled data however are available. Among 1,449 women who participated in the American Society of Breast Surgeons Mammosite Breast Brachytherapy Registry trial, the 5-year IBR rate was 3.8 percent, with good or excellent cosmetic results in 90.6 percent.[102, 132] The risk of infection with applicator-based brachytherapy is higher than other approaches due to the use of an indwelling foreign object during the course of radiation therapy and is reported at a rate of 3-16.5[133] percent; seroma is reported in 1.9-59.1 percent of patients.[132, 134-136] For comparison, the rate of infection and seroma for multicatheter interstitial brachytherapy is reported as 0-12.4 percent and 1 percent; for external beam radiotherapy, it is reported as 0-2.4 percent and 2-10 percent, respectively.[57, 70, 74, 76, 83, 137] In a large retrospective population-based cohort study of women treated with APBI using brachytherapy (predominantly single-entry catheter based approaches) compared with WBI, breast brachytherapy was associated with a significantly higher rate of subsequent mastectomy, infectious and noninfectious postoperative complications, breast pain, fat necrosis, and rib fracture.[138] Similar findings were observed in a large SEER (Surveillance, Epidemiology, and End Results)-Medicare analysis and in an analysis of younger women in a MarketScan insurance database, both of which reported a higher risk of subsequent mastectomy for brachytherapy compared to WBI, although the risk was lower among patients considered "suitable" according to ASTRO criteria and among those who received endocrine therapy.[133, 139] Although these results demonstrate the possibility of increased AEs with breast brachytherapy, the findings likely represent clinical practice during early implementation of the breast brachytherapy technique with patients treated before 2010. Currently there is a lack of high-quality data comparing applicator-based breast brachytherapy to WBI or to other APBI modalities, and it is unknown if similar findings would be observed with improved patient selection and more advanced treatment techniques with multilumen catheters that facilitate improved sparing of adjacent tissues while maintaining target coverage. This represents an area of interest for future study. The NSABP B-39/RTOG 0413 clinical trial enrolled 571 patients treated with APBI using brachytherapy (451 patients treated with single-entry brachytherapy and 120 patients with multicatheter interstitial brachytherapy). In an initial presentation of these results at the 2018 San Antonio Breast Cancer Symposium, both single-entry and multicatheter brachytherapy appeared to have a higher rate of 10-year IBR compared with WBI.[140] However, the findings between single-entry and multicatheter brachytherapy on this trial have not yet been

published, and while not a randomized comparison, represent an area of interest to inform optimal technique and patient selection.

In contrast to single-channel balloon-based brachytherapy for PBI, strut-adjusted volume implant (SAVI) and Contura are multi-channel devices that facilitate modulation of dose away from critical structures such as skin and chest wall while maintaining target coverage for PBI. Randomized data for this technique in comparison to WBI are lacking. In the Contura Multilumen Balloon Breast Brachytherapy Registry Trial, among 342 women from 23 institutions, the local recurrence-free survival was 97.8 percent at 3 years, with 88 percent with good or excellent cosmesis.[135] One study reported excellent disease control and toxicity profile among 102 patients treated with SAVI brachytherapy with short-term followup (median 1.8 years).[134] Another study with 132 patients from a single institution treated with SAVI brachytherapy reported a crude local recurrence rate of 4 percent with median followup of 1.7 years.[136]

It is plausible that nuances of treatment technique with single-entry catheter brachytherapy may significantly influence outcomes. For example, the applicator device may be placed intraoperatively at the time of lumpectomy, or it may be placed at a later time as a second procedure under ultrasound guidance. In contrast to the observation of higher IBR with delayed IORT in comparison to IORT completed at the time of lumpectomy,[41-50] there was no apparent difference in IBR for open cavity versus closed cavity placement of the brachytherapy applicator in one study;[132] this has not been formally evaluated in more recent data. Additionally, nuances of applicator placement and treatment planning have the potential to significantly influence the outcome of single-entry catheter brachytherapy. For example, the location of applicator placement relative to the tumor bed, as well as air pockets or seroma adjacent to the applicator, have the potential to significantly influence the dose distribution to adjacent breast and must be attentively managed both from a surgical perspective as well as during radiotherapy treatment planning. The importance of the expertise needed to obtain favorable outcomes is reflected in the observation of better outcomes in high-volume centers.[135] Selection criteria unique to applicator-based brachytherapy appear to be important, such as proximity to skin and tumor location within the breast that may be particularly challenging (i.e. subareolar location).

Most studies of applicator-based brachytherapy have evaluated a dose of 34 Gy in 10 fractions delivered twice daily. Two noteworthy studies evaluated a shorter regimen. In the TRIUMPH-T multicenter single-arm clinical trial, 200 women were treated with breast brachytherapy; 63 percent were treated with multilumen applicator-based brachytherapy, and the remainder with interstitial brachytherapy. With median 27 days from surgery to radiation, brachytherapy was delivered in 3 fractions to 22.5 Gy over 2-3 days. With short-term followup, this approach was associated with a low rate of toxicity and 97.3 percent good or excellent cosmetic results.[141] A single-institution prospective trial with 73 participants received multilumen catheter based APBI with 21.9 Gy delivered in three treatments given once daily. With 14-month followup, there were low rates of patient- and provider-reported adverse events, and good or excellent cosmesis in 95 percent.[142] Whereas most studies of catheter-based brachytherapy have placed the applicator as a separate procedure several weeks after lumpectomy, this study placed the brachytherapy catheter at the time of lumpectomy, which allowed patients to complete breast surgery and adjuvant radiotherapy within one week.

4.4. Limitations and Suggestions for Future Research

The clinical trials included in our aggregate analysis represent a variety of treatment techniques, including several methods of external beam radiotherapy (3DCRT, IMRT, proton therapy), brachytherapy (multi-catheter interstitial brachytherapy, single lumen applicator brachytherapy, multi-lumen applicator brachytherapy) and IORT (low-energy x-ray, electrons). Treatment outcomes of each individual radiation modality were insufficiently reported, which limited the ability to make comparisons between modalities.

Evaluation of outcomes according to patient, tumor and treatment subgroups was similarly limited by the available data. Many of the included clinical trials did not report subgroup analyses, and often the subgroups were not able to be combined for aggregate analysis. As a result, we were unable to assess many of the prespecified subgroups. Additionally, the results of subgroup analysis are limited by sample size and the risk of false-positive or false-negative findings. Our results from subgroup analysis may be informative in directing future areas of investigation but cannot definitively determine the magnitude of risk associated with each characteristic. Our results highlight the importance of further investigation to determine the outcomes of PBI among patients with adverse risk factors.

Although evaluation of cosmetic outcome was consistently reported using a 4-point scale to describe excellent, good, fair, and poor cosmesis (Table 2) in a relatively homogeneous population of favorable prognosis breast cancer, the reported rate of provider-assessed fair or poor cosmesis for WBI versus PBI spans a wide range. For example, three studies reported significantly higher rate of fair or poor cosmesis with WBI,[24, 70 51, 66-69] while another study[22, 52, 53] reported significantly higher rate of fair-poor cosmesis with PBI, with a spectrum of results between the two extremes. This variability between studies is reflected in the finding of statistically significant heterogeneity on 5-year and 10-year followup results for both provider-reported (I^2=89% and I^2=94%, respectively) and patient-reported cosmesis (I^2=56% and I^2=96%). Substantial heterogeneity, risk of bias and imprecision across studies, and lack of cosmetic outcome data from the largest study of PBI (NSABP B-39) limits the ability to draw conclusions regarding cosmetic outcomes in a comparison of PBI versus WBI.

We note that increased use of oncoplastic surgery in addition to lumpectomy may influence both eligibility for partial breast radiotherapy as well as the cosmetic outcome. In the reported studies of partial breast radiotherapy, oncoplastic tissue rearrangement was not specified as an exclusion criterion (with one exception)[40] but was not commonly used when the studies of PBI were developed. It is widely accepted that oncoplastic surgery typically precludes the ability to define the lumpectomy cavity for partial breast radiotherapy. The use of IORT for a boost after lumpectomy has been described,[143-145] and has been used as a method of delivering the boost in the setting of oncoplastic tissue rearrangement.[121, 146]

Several outcomes represent provider-rated or patient-reported measures, such as cosmesis, AEs, and quality of life. The comparison of PBI and WBI is not blinded to either clinicians or patients, and it is possible that the treatment assignment might have influenced perceptions of these subjective measures.

We could not statistically evaluate publication bias in all of the comparisons because the number of studies included in these comparisons was small (n<10). Only studies published in English language were included in this review.

There is a critical need to further evaluate patient reported outcomes and their influence on decision-making for breast radiotherapy. Similar oncologic outcomes between modalities, as reported here, suggest that key therapeutic differentiators for patients often lie within the

expected toxicity and quality of life. Some patients experiencing cancer are willing to sacrifice some efficacy of therapy for maintenance of quality of life, with substantial variation depending on factors such as age and baseline health status. Indeed, patients with favorable risk DCIS or older patients with early-stage breast cancer may opt for omission of radiotherapy altogether, thus limiting the potential impact of treatment on quality of life and financial toxicity, notwithstanding an increased but accepted risk of IBR.[3, 4] Patient valuation of benefits and risks of radiotherapy represent an important area for future study, particularly as radiotherapy omission has become a key area of ongoing investigation among younger patients with biologically favorable tumors, such as those enrolling on the DEBRA trial (NRG BR007).[147] Early results of the LUMINA trial[148] support the hypothesis that highly selected women with Luminal A-like tumors might have a sufficiently low rate of local recurrence to forego radiotherapy, provided that there is compliance with a complete course of endocrine therapy. Older women with favorable-risk breast cancer may prefer to avoid side effects related to endocrine therapy, and often choose a single treatment modality with either exclusive endocrine therapy or exclusive PBI alone.[149, 150] Comparison of these two approaches is currently being evaluated on the EUROPA clinical trial.[151] The landscape of options for early-stage favorable risk breast cancer is a key area of ongoing investigation that will significantly influence future decisions about tailoring the use of radiotherapy.

Additionally, with results from the FAST-Forward clinical trial showing non-inferior breast cancer outcomes and similar adverse effects with “ultrahypofractionated” WBI completed in 5 fractions compared to conventionally hypofractionated WBI,[10] the use of accelerated WBI is becoming more widely adopted in practice. The availability of “ultrahypofractionated” WBI narrows the distinction between PBI and WBI, since both can be completed within 1 week, with similar side effects and reduction in the financial burden of treatment. It is plausible that patients considered as “cautionary” or “unsuitable” for partial breast radiotherapy according to ASTRO criteria[26] might consider accelerated WBI rather than PBI. Notwithstanding this alternative, many patients may be motivated to pursue PBI to minimize radiation exposure of the breast and adjacent normal tissue, and thus defining the suitability of PBI in moderate risk subgroups remains an area of interest for future study.

Finally, radiotherapy technology has developed and dramatically changed over the past two to three decades, with a transition from 2D radiotherapy to routine use of 3D radiotherapy, IMRT, and other advanced planning technologies. These advancements result in improved dose homogeneity with fewer “hot spots,” which may lower the risk for adverse events. In addition, localization with image guidance enables smaller PTV expansions and improved treatment accuracy, which introduces challenges in comparisons that span a wide time interval of significant changes in radiotherapy technology and treatment. Although the volume of the treatment target relative to the breast, dose/fractionation schedule, and planning parameters are recognized as critically important to understand the risks related to treatment, these data were very limited or unavailable for many studies. Defining an optimal radiation dose, fractionation, and target size using contemporary techniques for treatment planning and image guidance, and characterizing the outcomes of that approach, represent key areas for future study, particularly for short regimens with daily treatment.

4.5. Conclusion

Among patients similar to those enrolled in clinical trials of PBI, there was no significant difference in the risk of IBR compared with WBI. PBI is associated with fewer acute adverse

effects and less financial toxicity than WBI delivered with standard fractionation. The risk of IBR among patients treated with PBI who have adverse clinical or pathologic features is unclear. IORT was found to have a significantly higher rate of IBR than WBI. Further investigation is needed to evaluate outcomes of PBI in moderate risk subgroups with less favorable clinicopathologic features and to define optimal radiation dose and treatment technique for PBI.

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Abbreviations and Acronyms

3DCRT	3-dimensional conformal external beam radiotherapy
AE	Adverse event
AHRQ	Agency for Health Care Research and Quality
APBI	Accelerated partial breast irradiation
ASTRO	American Society for Radiation Oncology
BCTOS	Breast Cancer Treatment Outcomes Scale
BMI	Body mass index
CI	Confidence interval
cm	Centimeter
CQ	Contextual Question
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
DCIS	Ductal carcinoma in situ
EORTC	European Organisation for Research and Treatment of Cancer
EQD2	Equivalent Dose in 2 Gy fractions
ER	Estrogen receptor
ESTRO	European Society for Radiotherapy and Oncology
FACT-B	Functional Assessment of Cancer Therapy-Breast
Gy	Gray
HER2	Human Epidermal Growth Factor Receptor 2
IBR	Ipsilateral breast recurrence
IMRT	Intensity-modulated radiation therapy
IORT	Intraoperative radiotherapy
IQR	Interquartile range
IRR	Incidence rate ratio
KQ	Key Question
kV	Kilovoltage
LENT-SOMA	Late Effects Normal Tissue Task Force- Subjective, Objective, Management, Analytic
mm	Millimeter
MV	Megavoltage
N/A	Not applicable
PBI	Partial breast irradiation
PICOTS	Populations, interventions, comparators, outcomes, timing, and settings
PR	Progesterone receptor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PTV	Planning target volume
RCT	Randomized clinical trial
RD	Risk difference
RR	Relative risk
RTOG	Radiation Therapy Oncology Group
SD	Standard deviation
SEADS	Supplemental Evidence and Data for Systematic Reviews
SEER	Surveillance, Epidemiology, and End Results
SF-36	Short Form (36) Health Survey
SOE	Strength of evidence
STEEP 2.0	Standardized Definitions for Efficacy End Points version 2.0
US	United States
V	Volume of a structure receiving a given dose of radiotherapy expressed as either a percentage of the prescription dose (e.g. V100%) or as a quantity of dose (e.g. V30Gy)
WBI	Whole breast irradiation

Appendix Contents

Appendixes

Tables

Figure

Appendix A. Search Strategy

Key Questions 1-2 and the Contextual Question

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials May 2022, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to June 29, 2022, Embase 1974 to 2022 June 30, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to June 30, 2022
Search Strategy:

#	Searches
1	exp Breast Neoplasms/rt [Radiotherapy]
2	exp Radiotherapy/
3	exp Radiation/
4	exp irradiation/
5	(APBI or brachytherap* or Contura or IMRT or IORT or irradiat* or linac or MammoSite or PBI or proton or radiation* or "radio therap*" or "radio treatment*" or radiotherap* or radiotreatment* or SAVI or "Single-entry catheter*" or WBI or "x ray*").ti,ab,hw,kw.
6	or/1-5
7	(((APBI or PBI or WBI) and breast) or "partial breast" or "whole breast").ti,ab,hw,kw.
8	6 and 7
9	("consensus development" or guideline* or "position statement*").ti,pt.
10	exp meta analysis/
11	exp Meta-Analysis as Topic/
12	exp "systematic review"/
13	((meta adj analys*) or (systematic* adj3 review*)).mp,pt.
14	10 or 11 or 12 or 13
15	exp controlled study/
16	exp Randomized Controlled Trial/
17	exp triple blind procedure/
18	exp Double-Blind Method/
19	exp Single-Blind Method/
20	exp latin square design/
21	randomised controlled trials.sd.
22	((control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or random*).mp,pt.
23	or/15-22

24 exp comparative study/
25 exp intervention studies/
26 exp Cross-Sectional Studies/
27 exp Cross-Over Studies/
28 exp Cohort Studies/
29 exp longitudinal study/
30 exp prospective study/
31 exp population research/
32 exp observational study/
33 exp clinical trial/
34 clinical study/
35 exp Evaluation Studies/
36 exp Evaluation Studies as Topic/
37 exp quantitative study/
38 exp validation studies/
39 exp experimental study/
40 exp quasi experimental study/
41 exp field study/
42 in vivo study/
43 exp panel study/
44 exp Pilot Projects/
45 exp pilot study/
46 exp prevention study/
47 exp replication study/
48 exp theoretical study/
49 exp Feasibility Studies/
50 exp trend study/
51 exp correlational study/
52 exp case-control studies/
53 exp confidence interval/
54 exp regression analysis/
55 exp proportional hazards model/
56 exp multivariate analysis/
57 exp qualitative study/
58 (multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or

cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or (population adj3 (stud* or survey* or analys* or research)) or "concurrent study" or "concurrent survey" or "concurrent analysis" or "incidence study" or "incidence survey" or "incidence analysis" or (("follow-up" or followup) adj (stud* or survey or analysis)) or ((observation or observational) adj (study or survey or analysis)) or "case study" or "case series" or "clinical series" or "case studies" or "clinical study" or "clinical trial" or (("phase 0" or "phase 1" or "phase I" or "phase 2" or "phase II" or "phase 3" or "phase III" or "phase 4" or "phase IV") adj5 (trial or study)) or "evaluation study" or "evaluation survey" or "evaluation analysis" or "quantitative study" or "quantitative analys*" or "numerical study" or "validation study" or "validation survey" or "validation analysis" or "experimental study" or "experimental analysis" or "quasi experimental study" or "quasi experimental analysis" or "quasiexperimental study" or "quasiexperimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or "pilot study" or "pilot survey" or "pilot analysis" or "pilot project" or ((prevention or preventive) adj3 (trial or study or analysis or survey)) or "replication study" or "replication analysis " or "replication trial" or "theoretical study" or "theoretical analysis " or "feasibility study" or "feasibility analysis" or "trend study" or "trend survey" or "trend analysis" or ((correlation* adj2 study) or (correlation* adj2 analys*)) or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or study or trial or pilot or "odds ratio" or "confidence interval" or "regression analysis" or "least square" or "least squares" or (hazard* adj (model* or analys* or regression or ratio or ratios)) or "Cox model" or "Cox multivariate analyses" or "Cox multivariate analysis" or "Cox regression" or "Cox survival analyses" or "Cox survival analysis" or "Cox survival model" or "change analysis" or ((study or trial or random* or control*) and compar*) or qualitative or ((retrospective or "ex post facto") not "single arm")).mp,pt.

59 or/24-58

60 or/9-59

61 8 and 60

62 limit 61 to yr="2000 -Current"

63 limit 62 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in CCTR,CDSR,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]

64 from 63 keep 1

65 (62 not 63) or 64

66 limit 65 to yr="2015 -Current"

67 remove duplicates from 66

68 65 not 66
69 remove duplicates from 68
70 67 or 69

Scopus

1 TITLE-ABS-KEY(APBI or brachytherap* or Contura or IMRT or IORT or irradiat* or linac or MammoSite or PBI or proton or radiation* or "radio therap*" or "radio treatment*" or radiotherap* or radiotreatment* or SAVI or "Single-entry catheter*" or WBI or "x ray*")
2 TITLE-ABS-KEY(((APBI or PBI or WBI) and breast) or "partial breast" or "whole breast")
3 TITLE-ABS-KEY("consensus development" or guideline* or "position statement*")
4 TITLE-ABS-KEY((meta W/1 analys*) or (systematic* W/3 review*))
5 TITLE-ABS-KEY((control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or random*)
6 TITLE-ABS-KEY(multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* W/2 study) or (intervention* W/2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or (population W/3 (stud* or survey* or analys* or research)) or "concurrent study" or "concurrent survey" or "concurrent analysis" or "incidence study" or "incidence survey" or "incidence analysis" or (("follow-up" or followup) W/1 (stud* or survey or analysis)) or ((observation or observational) W/1 (study or survey or analysis)) or "case study" or "case series" or "clinical series" or "case studies" or "clinical study" or "clinical trial" or (("phase 0" or "phase 1" or "phase I" or "phase 2" or "phase II" or "phase 3" or "phase III" or "phase 4" or "phase IV") W/5 (trial or study)) or "evaluation study" or "evaluation survey" or "evaluation analysis" or "quantitative study" or "quantitative analys*" or "numerical study" or "validation study" or "validation survey" or "validation analysis" or "experimental study" or "experimental analysis" or "quasi experimental study" or "quasi experimental analysis" or "quasiexperimental study" or "quasiexperimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or "pilot study" or "pilot survey" or "pilot analysis" or "pilot project" or ((prevention or preventive) W/3 (trial or study or analysis or survey)) or "replication study" or "replication analysis " or "replication trial" or "theoretical study" or "theoretical analysis " or "feasibility study" or "feasibility analysis" or "trend study" or "trend survey" or "trend analysis" or ((correlation* W/2 study) or (correlation* W/2 analys*)) or "case control study" or "case base study" or

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7 PUBYEAR AFT 1999

8 1 and 2 and (3 or 4 or 5 or 6) and 7

9 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

10 8 and not 9

11 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)

12 10 and not 11

Clinicaltrials.gov

Condition or disease:

Breast Cancer

Other Terms:

"partial breast" OR "whole breast" or APBI or PBI or WBI

Intervention/treatment

APBI OR brachytherapy OR Contura OR IMRT OR IORT OR irradiation OR linac OR MammoSite OR PBI OR proton OR radiation OR "radio therapy" OR "radio treatment" OR radiotherapy OR radiotreatment OR SAVI OR "Single-entry catheter" OR WBI OR "x ray"

First Posted

01/01/2000 to 07/01/2022

Contextual Question: Financial Toxicity

For the Contextual Question, we developed the following strategy in addition to the one listed above.

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials May 2022, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to June 29, 2022, Embase 1974 to 2022 June 30, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to June 30, 2022
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2	exp Radiotherapy/

3 exp Radiation/

4 exp irradiation/

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6 or/1-5

7 (((APBI or PBI or WBI) and breast) or “partial breast” or “whole breast”).ti,ab,hw,kw.

8 6 and 7

9 ((patient* and (cost or costs or economic* or expense* or financ* or expenditure*) and (stress* or anxiet* or impact* or burden*)) or “financial toxicity”).ti,ab,hw,kw.

10 8 and 9

11 exp meta analysis/

12 exp Meta-Analysis as Topic/

13 exp “systematic review”/

14 ((meta adj analys*) or (systematic* adj3 review*)).mp,pt.

15 11 or 12 or 13 or 14

16 exp controlled study/

17 exp Randomized Controlled Trial/

18 exp triple blind procedure/

19 exp Double-Blind Method/

20 exp Single-Blind Method/

21 exp latin square design/

22 randomised controlled trials.sd.

23 ((control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or “pragmatic clinical trial” or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or “latin square” or random*).mp,pt.

24 or/16-23

25 exp comparative study/

26 exp intervention studies/

27 exp Cross-Sectional Studies/

28 exp Cross-Over Studies/

29 exp Cohort Studies/

30 exp longitudinal study/

31 exp prospective study/

32 exp population research/

33 exp observational study/
34 exp clinical trial/
35 clinical study/
36 exp Evaluation Studies/
37 exp Evaluation Studies as Topic/
38 exp quantitative study/
39 exp validation studies/
40 exp experimental study/
41 exp quasi experimental study/
42 exp field study/
43 in vivo study/
44 exp panel study/
45 exp Pilot Projects/
46 exp pilot study/
47 exp prevention study/
48 exp replication study/
49 exp theoretical study/
50 exp Feasibility Studies/
51 exp trend study/
52 exp correlational study/
53 exp case-control studies/
54 exp confidence interval/
55 exp regression analysis/
56 exp proportional hazards model/
57 exp multivariate analysis/
58 exp qualitative study/
59 exp "Surveys and Questionnaires"/
60 (multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or (population adj3 (stud* or survey* or analys* or research)) or "concurrent study" or "concurrent survey" or "concurrent analysis" or "incidence study" or "incidence survey" or "incidence analysis" or (("follow-up" or followup) adj (stud* or survey or analysis)) or ((observation or observational) adj (study or survey or analysis)) or "case study"

or “case series” or “clinical series” or “case studies” or “clinical study” or “clinical trial” or ((“phase 0” or “phase 1” or “phase I” or “phase 2” or “phase II” or “phase 3” or “phase III” or “phase 4” or “phase IV”) adj5 (trial or study)) or “evaluation study” or “evaluation survey” or “evaluation analysis” or “quantitative study” or “quantitative analys*” or “numerical study” or “validation study” or “validation survey” or “validation analysis” or “experimental study” or “experimental analysis” or “quasi experimental study” or “quasi experimental analysis” or “quasiexperimental study” or “quasiexperimental analysis” or “field study” or “field survey” or “field analysis” or “in vivo study” or “in vivo analysis” or “panel study” or “panel survey” or “panel analysis” or “pilot study” or “pilot survey” or “pilot analysis” or “pilot project” or ((prevention or preventive) adj3 (trial or study or analysis or survey)) or “replication study” or “replication analysis “ or “replication trial” or “theoretical study” or “theoretical analysis “ or “feasibility study” or “feasibility analysis” or “trend study” or “trend survey” or “trend analysis” or ((correlation* adj2 study) or (correlation* adj2 analys*)) or “case control study” or “case base study” or “case referrent study” or “case referent study” or “case referent study” or “case compeer study” or “case comparison study” or “matched case control” or “multicenter study” or “multi-center study” or study or trial or pilot or “odds ratio” or “confidence interval” or “regression analysis” or “least square” or “least squares” or (hazard* adj (model* or analys* or regression or ratio or ratios)) or “Cox model” or “Cox multivariate analyses” or “Cox multivariate analysis” or “Cox regression” or “Cox survival analyses” or “Cox survival analysis” or “Cox survival model” or “change analysis” or ((study or trial or random* or control*) and compar*) or qualitative or ((retrospective or “ex post facto”) not “single arm”) or “case study” or “case series” or “clinical series” or “case studies” or survey* or questionnaire*).mp,pt.

61 or/11-60

62 10 and 61

63 limit 62 to yr=”2000 -Current”

64 limit 63 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in CCTR,CDSR,Embase,Ovid MEDLINE®,Ovid MEDLINE® Daily Update,Ovid MEDLINE® PubMed not MEDLINE,Ovid MEDLINE® In-Process,Ovid MEDLINE® Publisher; records were retained]

65 63 not 64

66 remove duplicates from 65

Scopus

1 TITLE-ABS-KEY(APBI or brachytherap* or Contura or IMRT or IORT or irradiat* or linac or MammoSite or PBI or proton or radiation* or "radio therap*" or "radio

treatment*" or radiotherap* or radiotreatment* or SAVI or "Single-entry catheter*" or WBI or "x ray*")

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3 TITLE-ABS-KEY((patient* and (cost or costs or economic* or expense* or financ* or expenditure*) and (stress* or anxiet* or impact* or burden*)) OR "financial toxicity")

4 TITLE-ABS-KEY((meta W/1 analys*) or (systematic* W/3 review*))

5 TITLE-ABS-KEY((control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or random*)

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not "single arm") or "case study" OR "case series" OR "clinical series" OR "case studies" or survey* or questionnaire*)

7 PUBYEAR AFT 1999 AND LANGUAGE(english)

8 1 and 2 and 3 and (4 or 5 or 6) and 7

9 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

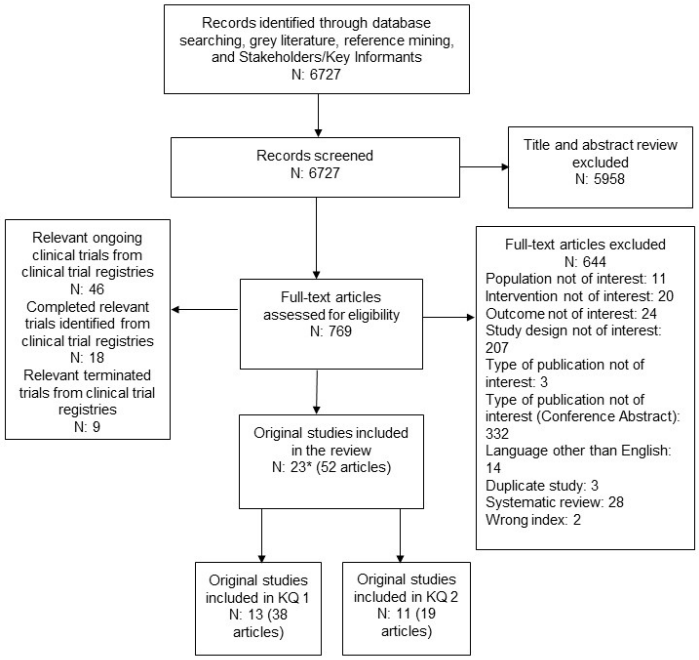
10 8 and not 9

11 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)

12 10 and not 11

Appendix B. Flow Chart

Figure B-1. Flow chart for Key Question 1 and Key Question 2



Abbreviations: KQ = Key Question

*: One study[1] addresses both Key Question 1 and Key Question 2

Appendix C. Excluded Studies

1. Hannoun-Levi J-M, Montagne L, Sumodhee S, et al. APBI verssus Ultra-APBI in the elderly with low-risk breast cancer: a comparative analysis of oncological outcome and late toxicity. Int J Radiat Oncol Biol Phys. 2021 Apr 06;06:06. doi: 10.1016/j.ijrobp.2021.03.052. PMID: 33831490. [Ineligible study design]
2. Laplana M, Cozzi S, Najjari D, et al. Five-year results of accelerated partial breast irradiation: a single-institution retrospective review of 289 cases. Brachytherapy. 2021 Mar 30;30:30. doi: 10.1016/j.brachy.2021.02.003. PMID: 33810984. [Ineligible study design]
3. Shah C, Jia X, Hobbs BP, et al. Outcomes with partial breast irradiation vs. whole breast irradiation: a meta-analysis. Ann Surg Oncol. 2021 Jan 03;03:03. doi: 10.1245/s10434-020-09447-w. PMID: 33393051. [Systematic review]
4. Klautke G. [Partial breast irradiation vs. whole breast irradiation: a meta-analysis regarding local control]. Strahlenther Onkol. 2021 Jul;197(7):655-6. doi: 10.1007/s00066-021-01787-0. PMID: 33903922. [Language other than English]
5. Hepel JT, Leonard KL, Rivard M, et al. Multi-institutional registry study evaluating the feasibility and toxicity of accelerated partial breast irradiation using noninvasive image-guided breast brachytherapy. Brachytherapy. 2021 May-Jun;20(3):631-7. doi: 10.1016/j.brachy.2021.01.002. PMID: 33642174. [Ineligible study design]
6. Arthur DW, Winter KA, Kuerer HM, et al. Effectiveness of breast-conserving surgery and 3-dimensional conformal partial breast reirradiation for recurrence of breast cancer in the ipsilateral breast: the NRG Oncology/RTOG 1014 phase 2 clinical trial. JAMA Oncol. 2020 Jan 01;6(1):75-82. doi: 10.1001/jamaoncol.2019.4320. PMID: 31750868. [Ineligible Population]
7. Yang H-Y, Tu C-W, Chen C-C, et al. Sole adjuvant intraoperative breast radiotherapy in Taiwan: a single-center experience. Breast Cancer Res. 2021 Apr 01;23(1):43. doi: 10.1186/s13058-021-01421-y. PMID: 33794958. [Ineligible study design]
8. Guinot JL, Gonzalez-Perez V, Meszaros N, et al. Very accelerated partial breast irradiation phase I-II multicenter trial (VAPBI): feasibility and early results. Brachytherapy. 2021 Mar-Apr;20(2):332-8. doi: 10.1016/j.brachy.2020.10.010. PMID: 33223449. [Ineligible study design]
9. Boutrus RR, El Sherif S, Abdelazim Y, et al. Once daily versus twice daily external beam accelerated partial breast irradiation: a randomized prospective study. Int J Radiat Oncol Biol Phys. 2021 Apr 01;109(5):1296-300. doi: 10.1016/j.ijrobp.2020.11.044. PMID: 33714527. [Ineligible study design]
10. Xiang X, Ding Z, Feng L, et al. A meta-analysis of the efficacy and safety of accelerated partial breast irradiation versus whole-breast irradiation for early-stage breast cancer. Radiat. 2021 Feb 02;16(1):24. doi: 10.1186/s13014-021-01752-2. PMID: 33531014. [Systematic review]
11. Sumodhee S, Pujalte M, Gal J, et al. Accelerated partial breast irradiation in the elderly: 8-year oncological outcomes and prognostic factors. Brachytherapy. 2021 Jan-Feb;20(1):146-54. doi: 10.1016/j.brachy.2020.08.012. PMID: 33132071. [Ineligible study design]
12. Joseph K, Vos LJ, Gabos Z, et al. Skin toxicity in early breast cancer patients treated with field-in-field breast intensity-modulated radiotherapy versus helical inverse breast intensity-modulated radiotherapy: results of a phase iii randomised controlled trial. Clin Oncol (R Coll Radiol). 2021 Jan;33(1):30-9. doi: 10.1016/j.clon.2020.07.005. PMID: 32711920. [Ineligible Intervention]
13. Goulding A, Asmar L, Wang Y, et al. Outcomes after accelerated partial breast irradiation in women with triple negative subtype and other "high risk" variables categorized as cautionary in the ASTRO guidelines. Front. 2021;11:617439. doi: 10.3389/fonc.2021.617439. PMID: 33777758. [Ineligible study design]

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Appendix D. Characteristics of Included Studies

Table D.1. Characteristics of included studies. KQ 1: PBI versus WBI

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Budapest,[2] 2007,[1, 3] 2013,[4] 2021[5]	Noninferiority RCT in Hungary 07/1998 to 05/2004	APBI (multi-catheter interstitial brachytherapy or APBI (3DCRT)	Inclusion: Patients with wide excision with microscopically negative surgical margins; unifocal tumor; primary tumor size ≤20 mm (pT1); cN0, pN0, or pN1mi (single nodal micrometastasis > 0.2mm and ≤ 2.0 mm) axillary status; and histologic grade 2 or less. Exclusion: Patients aged ≤ 40 years; bilateral breast carcinoma; prior uni- or contralateral breast cancer; concomitant or previous other malignancies (except basal cell carcinoma of the skin); pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; or the presence of an extensive intraductal component.	Median 17	128 patients aged 59 years (Range: 30-84 years); tumor size: 1.3 cm (<1.5 cm: 36.5%, 1.1-2 cm: 63.3%); nodal status (N0: 94.5%, N1; 2.3%, NX/unknown: 3.2%); estrogen receptor positive: 90.6%; progesterone receptor positive: 81.2%; lymphovascular invasion: 2.3%; unifocal: 100%; surgical margins (<2 mm: 0%; 2-10 mm: 58.6%; >10 mm: 37.5%).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Budapest,[2] 2007,[1,3] 2013,[4] 2021,[5] (continued)	Noninferiority RCT in Hungary 07/1998 to 05/2004	WBI	Inclusion: Patients with wide excision with microscopically negative surgical margins; unifocal tumor; primary tumor size ≤20 mm (pT1); cN0, pN0, or pN1mi (single nodal micrometastasis > 0.2mm and ≤ 2.0 mm) axillary status; and histologic grade 2 or less. Exclusion: Patients aged ≤ 40 years; bilateral breast carcinoma; prior uni- or contralateral breast cancer; concomitant or previous other malignancies (except basal cell carcinoma of the skin); pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; or the presence of an extensive intraductal component.	Median 17	130 patients aged 58 years (Range: 31-80 years); tumor size: 1.3 cm (<1.5 cm: 29.2%, 1.1-2 cm: 70.8%); nodal status (N0: 94.6%, N1; 4.6%, NX/unknown: 0.8%); estrogen receptor positive: 86.9%; progesterone receptor positive: 78.4%; lymphovascular invasion: 4.6%; unifocal: 100%; surgical margins (<2 mm: 0.8%; 2-10 mm: 58.5%; >10 mm: 26.1%).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Dodwell, 2005[6]	RCT in the United Kingdom, 07/1986 to 06/1990	Nonaccelerated PBI (3DCRT/2DRT, and electrons)	Inclusion: Women with pT1/T2 pN0/N1 tumors; underwent local excision of their tumor and level 2 axillary lymph node dissection; must have clear margins defined as rim of normal tissue; underwent perioperative chemotherapy treatment. Exclusion: NR	Median 8	84 patients aged 52 years (Range: 25-69 years); tumor size: 1.9 cm (Range 0.3-4.5 cm); Invasive ductal carcinoma: 86%; grade 3: 23%; positive nodes: 41%.
	RCT in the United Kingdom, 07/1986 to 06/1990	WBI	Inclusion: Women with pT1/T2 pN0/N1 tumors; underwent local excision of their tumor and level 2 axillary lymph node dissection; must have clear margins defined as rim of normal tissue; underwent perioperative chemotherapy treatment. Exclusion: NR	Median 8	90 patients aged 51.5 years (Range: 23-68 years); tumor size: 2.1 cm (Range 0.5-4.5 cm); Invasive ductal carcinoma: 83%; grade 3: 24%; positive nodes: 31%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
ELIOT,[7, 8] NCT01849133	Equivalence RCT in Italy, 11/2000 to 12/2007	APBI (IORT)	Inclusion: Patients aged 48–75 years; early breast cancer; a maximum tumor diameter up to 2.5 cm; and suitable for breast-conserving therapy. Exclusion: NR	Median 12.4	651 patients aged 48-75 years (Age ≤ 50: 7%; Age 51-60 years: 44%,Age 61-70 years: 40%; Age >70 years: 10%); grade 1: 31%; grade 2: 48%; grade 3: 20%; tumor size (≤1 cm: 31%, 1.1-2 cm; 57%, >2 cm:13%); invasive ductal carcinoma: 81%; invasive lobular carcinoma: 8%; other histologic subtype: 8%; nodal status (N0: 74%, N1: 21%, ≥4 positive nodes: 5%); Luminal A: 40%; Luminal B: 51%; Non-Luminal: 3%; estrogen receptor positive: 90%; progesterone receptor positive: 76%; triple negative: 7%; systemic therapy (none; 4%, endocrine: 75%, chemotherapy: 8%, endocrine and chemotherapy: 13%); Ki-67 <20%: 62%; Ki-67 >20%: 38%
	Equivalence RCT in Italy, 11/2000 to 12/2007	WBI	Inclusion: Patients aged 48–75 years; early breast cancer; a maximum tumor diameter up to 2.5 cm; and suitable for breast-conserving therapy. Exclusion: NR	Median 12.4	654 patients aged 48-75 years (Age ≤ 50:7%; Age 51-60 years: 41%, Age 61-70 years: 41%; Age >70 years: 11%); grade 1: 25%; grade 2: 52%; grade 3: 23%; tumor size (≤1 cm: 30%, 1.1-2 cm: 54%, >2 cm:16%); invasive ductal carcinoma: 79%; invasive lobular carcinoma: 9%; other histologic subtype: 9%; nodal status (N0: 73%, N1: 21%, ≥4 positive nodes: 6%); Luminal A: 37%; Luminal B: 55%; Non-Luminal: 4%; estrogen receptor positive: 91%; progesterone receptor positive: 80%; triple negative: 5%; systemic therapy (none: 4%, endocrine: 74%, chemotherapy: 7%, endocrine and chemotherapy: 15%); %); Ki-67 <20%: 59%; Ki-67 >20%: 41%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Florence,[9-13] NCT02104895	Equivalence RCT in Italy, 03/2005 to 06/2013	APBI (IMRT)	Inclusion: Patients aged > 40 years; early breast cancer (maximum diameter 2.5 cm); suitable for breast-conserving surgery; enrolled patients had to be able to complete prescribed treatments and to adhere to trial followup program. Exclusion: Patients with previously diagnosed solid tumors; left ventricular ejection fraction <50% as measured by echocardiography or a history of active angina, myocardial infarction, or other cardiovascular disease; forced expiratory volume in 1 second <1 Liter/minute; extensive intraductal carcinoma; multiple foci cancer; final surgical margins <5 mm; and the absence of surgical clips in tumor bed.	Median 10.7	260 patients aged (Age ≤ 50 years:15.8%; Age 51-60 years: 23.5%, Age 61-70 years: 38.1%; Age >70 years: 22.6%); grade 1: 47.7%; grade 2: 42.3%; grade 3: 10%; invasive ductal carcinoma: 56.2%; invasive lobular carcinoma: 8.1%; DCIS: 8.8%; other histologic subtype: 21.1%; nodal status (N0: 89.2%, N1: 7.3%); ASTRO risk (suitable: 51.2%, cautionary: 28.5%, unsuitable: 20.3%, low: 73.1%, intermediate: 15.8%, high: 11.1%); estrogen receptor positive: 95.4%; progesterone receptor positive: 89.2%; HER2 positive: 2.5%; systemic therapy (none; 35.8%, endocrine: 59.6%, chemotherapy: 1.9%, endocrine and chemotherapy: 2.7%); Ki-67 <20%: 79.4%; Ki-67 >20%: 20.6%.
	Equivalence RCT in Italy, 03/2005 to 06/2013	WBI	Inclusion: Patients aged > 40 years; early breast cancer (maximum diameter 2.5 cm); suitable for breast-conserving surgery; enrolled patients had to be able to complete prescribed treatments and to adhere to trial followup program. Exclusion: Patients with previously diagnosed solid tumors; left ventricular ejection fraction <50% as measured by echocardiography or a history of active angina, myocardial infarction, or other cardiovascular disease; forced expiratory volume in 1 second <1 Liter/minute; extensive intraductal carcinoma; multiple foci cancer; final surgical margins <5 mm; and the absence of surgical clips in tumor bed.	Median 10.7	260 patients aged (Age ≤ 50 years:17.3%; Age 51-60 years: 29.2%, Age 61-70 years: 31.2%; Age >70 years: 22.3%); grade 1: 39.6%; grade 2: 47.7%; grade 3: 12.7%; invasive ductal carcinoma: 58.8%; invasive lobular carcinoma: 11.2%; DCIS: 12.3%; other histologic subtype: 10.8%; nodal status (N0: 81.9%, N1: 12.7%); ASTRO risk (suitable: 43.5%, cautionary: 30.4%, unsuitable: 26.1%, low: 63.8%, intermediate: 18.1%, high: 18.1%); estrogen receptor positive: 95.8%; progesterone receptor positive: 90.4%; HER2 positive: 5.6%; systemic therapy (none; 28.8%, endocrine: 62.3%, chemotherapy: 1.2%, endocrine and chemotherapy: 7.7%); Ki-67 <20%: 72.2%; Ki-67 >20%: 27.8%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
GEC-ESTRO,[14-17] NCT00402519	Noninferiority RCT in Austria, the Czech Republic, Germany, Hungary, Poland, Spain, and Switzerland, 04/20/2004 to 07/30/2009	APBI (multi-catheter interstitial brachytherapy)	Inclusion: Patients aged ≥ 40 years; had pTis or pT1–2a (lesions of ≤3 cm diameter); pN0/pNmi, and M0 breast cancer (stage 0, I, and IIA); had undergone local excision of the breast tumor with microscopically clear resection margins of at least 2 mm in any direction (in cases of invasive lobular carcinoma or DCIS, at least 5 mm); and had no lymph or blood-vessel invasion. In addition to low or intermediate risk DCIS lesions (Van Nuys prognostic index <8). For patients with invasive carcinoma, either an axillary dissection with minimum of six nodes in the specimen or a negative sentinel node was required; in case of pure DCIS, axillary staging, sentinel lymph node biopsy was optional. Exclusion: Patients younger than 40 years; had multiple tumor foci or an extensive intraductal component; Paget's disease or pathological skin involvement; synchronous or previous breast cancer; a history of other malignant disease; and pregnant or lactating patients.	Median 6.6	655 patients aged 62 years (IQR: 54-67 years); postmenopausal 83%; grade 1: 39%; grade 2: 50%; grade 3: 9%; unknown grade: 1%; tumor size: 1.2 cm (Range: 0.9-1.7 cm); invasive ductal carcinoma: 72%; lobular carcinoma: 13%; tubular: 6%; mucinous 2%; papillary: 1%; medullary <1%; unknown histologic subtype: 6%; nodal status (N0: 94%, N1: 1%, NX/unknown: 5%); estrogen receptor positive: 91.5%; progesterone receptor positive: 81.4%; combined ER/PR positive: 81%; systemic therapy (none: 9%, endocrine: 87%, chemotherapy: 10%); surgical free margins: 0.8 cm (Range: 0.2-4 cm).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
GEC-ESTRO,[14-17] NCT00402519 (continued)	Noninferiority RCT in Austria, the Czech Republic, Germany, Hungary, Poland, Spain, and Switzerland, 04/20/2004 to 07/30/2009	WBI	Inclusion: Patients aged ≥ 40 years; had pTis or pT1–2a (lesions of ≤3 cm diameter); pN0/pNmi, and M0 breast cancer (stage 0, I, and IIA); had undergone local excision of the breast tumor with microscopically clear resection margins of at least 2 mm in any direction (in cases of invasive lobular carcinoma or DCIS, at least 5 mm); and had no lymph or blood-vessel invasion. In addition to low or intermediate risk DCIS lesions (Van Nuys prognostic index <8). For patients with invasive carcinoma, either an axillary dissection with minimum of six nodes in the specimen or a negative sentinel node was required; in case of pure DCIS, axillary staging, sentinel lymph node biopsy was optional. Exclusion: Patients younger than 40 years; had multiple tumor foci or an extensive intraductal component; Paget's disease or pathological skin involvement; synchronous or previous breast cancer; a history of other malignant disease; and pregnant or lactating patients.	Median 6.6	673 patients aged 62 years (IQR: 54-68 years); postmenopausal: 83%; grade 1: 39%; grade 2: 52%; grade 3: 8%; unknown grade: 1%; tumor size: 1.2 cm (Range: 0.9-1.7 cm); invasive ductal carcinoma: 77%; lobular carcinoma: 9%; tubular: 7%; mucinous: 2%; papillary: 1%; medullary: <1%; unknown histologic subtype: 4%; nodal status (N0: 95%, N1: 1%, NX/unknown: 4%); estrogen receptor positive: 91.3%; progesterone receptor positive: 82.2%; combined ER/PR positive: 81%; systemic therapy (none: 8%, endocrine 87%, chemotherapy 12%); surgical free margins: 0.7 cm (Range: 0.2-2.5 cm).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
HYPAB[18]	RCT in Italy, 01/2015 to 01/2018	APBI (IMRT)	Inclusion: Postmenopausal women with biopsy-proven infiltrating breast cancer; clinically negative axilla; single T1-2 tumors; treated with breast-conserving surgery and sentinel node(s) biopsy; estrogen receptor positive; unicentric disease; clear surgical margins (> 5mm); no *BRCA1/2* mutation, any grade; no extensive intraductal component (>25%). Exclusion: Patients with prior thoracic radiation therapy; oncoplastic surgery; multicentric cancer; autoimmune disease; vasculitis; collagenopathy or scleroderma.	Median 3	82 patients aged 64 years (Range: 44-76 years); postmenopausal: 100%; grade 1: 8%; grade 2: 39%; grade 3: 1%; DCIS grade (not present: 10%, minimal: 32%, moderate: 6%); tumor size: 1.1 cm (Range: 0.2-2.4 cm); histologic subtype (nonspecial type: 38%, other histotype: 9%); estrogen receptor positive: 90%; progesterone receptor positive: 70%; lymphovascular invasion: 3%; systemic therapy: 96%; Ki-67 >20%: 10%.
	RCT in Italy, 01/2015 to 01/2018	WBI	Inclusion: Postmenopausal women with biopsy-proven infiltrating breast cancer; clinically negative axilla; single T1-2 tumors; treated with breast-conserving surgery and sentinel node(s) biopsy; estrogen receptor positive; unicentric disease; clear surgical margins (> 5mm); no *BRCA1/2* mutation, any grade; no extensive intraductal component (>25%). Exclusion: Patients with prior thoracic radiation therapy; oncoplastic surgery; multicentric cancer; autoimmune disease; vasculitis; collagenopathy or scleroderma.	Median 3	90 patients aged 64 years (Range: 50-76 years); grade 1: 4%; grade 2: 46%; grade 3: 2%; DCIS grade (not present: 13%, minimal: 34%, moderate: 5%); tumor size: 1.1 cm (Range: 0.1-2.5 cm); histologic subtype (nonspecial type: 36%, other histotype: 17%); estrogen receptor positive: 90%; progesterone receptor positive: 80%; lymphovascular invasion: 6%; systemic therapy: 98%; Ki-67 >20%: 11%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
NSABP B-39/RTOG 0413,[19] NCT00103181	Noninferiority RCT in the United States of America, 03/21/2005 to 04/16/2013	APBI (single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, 3DCRT)	Inclusion: Patients older than 18 years; received lumpectomy for stage 0 cancer (i.e., DCIS); stage I or II (tumor size ≤3 cm) invasive adenocarcinoma of the breast with no evidence of distant metastases; life expectancy of at least 10 years; surgical resection margins free of cancer, including DCIS; primary tumor must have been tested for estrogen receptor, and in some cases for progesterone receptor; up to three axillary lymph nodes could be positive for metastases; patients with all histologies and multifocal breast cancers; and had to be randomly assigned to groups within 42 days of the most recent surgery. Exclusion: NR	Median 10.2	2,107 patients aged 54 years (IQR: 47-64 years); Age ≤ 50 years: 38%; Age 50-70 years: 49%; Age >70 years: 13%; African American: 7%; White: 90%; Asian: 1%; Hispanic: 4%; other race/ethnicity: 1%; postmenopausal: 61%; grade 1: 28%; grade 2: 37%; grade 3: 26%; unknown grade: 9%; DCIS grade entire population (low grade: 14%, moderate grade: 25%, high grade: 28%, unknown: 32%); tumor size invasive only (≤1 cm: 28%, 1.1-2 cm: 31%, > 2 cm: 9%), DCIS: 25%; unknown tumor size: 8%; invasive ductal carcinoma: 61%, invasive lobular carcinoma: 5%; DCIS: 25%; other histologic subtype: 2%; nodal status (N0: 90%, N1: 8%, NX/unknown: <1%, 2 positive nodes: 2%, 3 positive nodes: 1%, unknown number of positive nodes: <1%); combined ER/PR positive: 81%; systemic therapy (endocrine: 85%, chemotherapy: 29%); unifocal 92%; multifocal 8%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
NSABP B-39/RTOG 0413,[19] NCT00103181 (continued)	Noninferiority RCT in the United States of America, 03/21/2005 to 04/16/2013	WBI	Inclusion: Patients older than 18 years; received lumpectomy for stage 0 cancer (i.e., DCIS); stage I or II (tumor size ≤3 cm) invasive adenocarcinoma of the breast with no evidence of distant metastases; life expectancy of at least 10 years; surgical resection margins free of cancer, including DCIS; primary tumor must have been tested for estrogen receptor, and in some cases for progesterone receptor; up to three axillary lymph nodes could be positive for metastases; patients with all histologies and multifocal breast cancers; and had to be randomly assigned to groups within 42 days of the most recent surgery. Exclusion: NR	Median 10.2	2,109 patients aged 54 years (IQR: 47-64 years); Age ≤ 50 years: 38%; Age 50-70 years: 50%; Age >70 years: 12%; African American: 7%; White: 89%; Asian: 2%; Hispanic: 4%; others: <1%; postmenopausal 61%; grade 1: 28%; grade 2: 35%; grade 3: 27%; unknown grade: 10%; DCIS grade entire population (low grade: 14%, moderate grade: 25%, high grade: 28%, unknown: 32%); tumor size invasive only (≤1 cm: 28%, 1.1-2 cm: 30%, > 2 cm: 9%), DCIS: 25%; unknown tumor size: 8%; invasive ductal carcinoma 61%, invasive lobular carcinoma 4%; DCIS 24%; other histologic subtype 2%; nodal status (N0: 90%, N1: 8%, NX/unknown: 1%, 2 positive nodes: 2%, 3 positive nodes: <1%, unknown number of positive nodes: 1%); combined ER/PR positive: 81%; systemic therapy (endocrine: 82%, chemotherapy: 29%); unifocal: 92%; multifocal: 8%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
UK IMPORT LOW,[20, 21] ISRCTN12852634	Noninferiority RCT in the United Kingdom, 05/03/2007 to 10/05/2010	Nonaccelerated PBI (3DCRT)	Inclusion: Patients aged ≥ 50 years; undergone breast-conserving surgery for unifocal invasive ductal adenocarcinoma of grade 1–3; tumor size of 3 cm or less (pT1–2); negative axillary node or 1-3 positive nodes (pN0–1); and minimum microscopic margins of non-cancerous tissue of 2 mm or more. Exclusion: Patients with distant metastases; a previous malignancy of any kind (unless non-melanomatous skin cancer); undergone a mastectomy or received neoadjuvant chemotherapy or concurrent adjuvant chemoradiotherapy.	Median 6	669 patients aged 62 years (IQR: 57-67 years); grade 1: 43%; grade 2: 48%; grade 3: 9%; tumor size: 1.2 cm (Range 0.8-1.6 cm; invasive ductal carcinoma: 85%; mixed carcinoma: 3%; other histologic subtype: 12%; nodal status (N0: 98%, number of positive nodes: 2%); axillary lymph node dissection >99%; estrogen receptor positive: 95%; progesterone receptor positive: 80%; HER2 positive: 6%; lymphovascular invasion: 7%; systemic therapy (endocrine: 91%, chemotherapy: 5%); other treatment: Trastuzumab: 2%; unifocal: 100%.
	Noninferiority RCT in the United Kingdom, 05/03/2007 to 10/05/2010	WBI	Inclusion: Patients aged ≥ 50 years; undergone breast-conserving surgery for unifocal invasive ductal adenocarcinoma of grade 1–3 tumor size of 3 cm or less (pT1–2); negative axillary node or 1-3 positive nodes (pN0–1); and minimum microscopic margins of non-cancerous tissue of 2 mm or more. Exclusion: Patients with distant metastases; a previous malignancy of any kind (unless non-melanomatous skin cancer); undergone a mastectomy or received neoadjuvant chemotherapy or concurrent adjuvant chemoradiotherapy.	Median 6	674 patients aged 62 years (IQR: 57-67 years); grade 1: 44%; grade 2: 46%; grade 3: 10%; tumor size: 1.2 cm (Range: 08-1.5); invasive ductal carcinoma: 86%; mixed carcinoma: 2%; other histologic subtype: 12%; nodal status (N0: 96%, number of positive nodes: 4%); axillary lymph node dissection: >99%; estrogen receptor positive: 95%; progesterone receptor positive: 81%; HER2 positive: 4%; lymphovascular invasion: 7%; systemic therapy (endocrine: 91%, chemotherapy: 4%); other treatment: Trastuzumab: 1%; unifocal: 100%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
RAPID,[22-24] NCT00282035	RCT in Canada, Australia, and New Zealand, 02/2006 to 07/2011	PBI (3DCRT)	Inclusion: Aged 40 years or older; DCIS or invasive ductal carcinoma who had undergone breast conserving surgery; microscopically clear margins and negative axillary lymph nodes measured by sentinel node biopsy or axillary dissection for those with invasive disease, and by clinical examination for those with DCIS alone; isolated tumor cells or micrometastases ≤ 2 mm in the lymph nodes. Exclusion: Tumor size larger than 3 cm; lobular carcinoma; more than one primary tumor in different quadrants of the breast; a radiotherapy plan that did not meet protocol-defined dose volume constraints for PBI	Median 8.6	1,070 patients aged 61 years (IQR: 54-68 years); grade 1: 44%; grade 2: 40%; grade 3: 15%; unknown grade: 1%; tumor size (<1.5 cm: 70%, ≥1.5 cm: 30%); invasive ductal carcinoma: 82%; DCIS: 18%; nodal status (N0: 99%, number of positive nodes: <1%); sentinel lymph node biopsy: 73%; axillary lymph node dissection: 26%; unknown nodal assessment: 1%; estrogen receptor positive: 91%; HER2 positive: 6%; lymphovascular invasion: 7%; systemic therapy (none: 34%, endocrine: 61%, chemotherapy: 12%).
	RCT in Canada, Australia, and New Zealand, 02/2006 to 07/2011	WBI	Inclusion: Aged 40 years or older; DCIS or invasive ductal carcinoma who had undergone breast conserving surgery; microscopically clear margins and negative axillary lymph nodes measured by sentinel node biopsy or axillary dissection for those with invasive disease, and by clinical examination for those with DCIS alone; isolated tumor cells or micrometastases ≤ 2 mm in the lymph nodes. Exclusion: Tumor size larger than 3 cm; lobular carcinoma; more than one primary tumor in different quadrants of the breast; a radiotherapy plan that did not meet protocol-defined dose volume constraints for PBI	Median 8.6	1,065 patients aged 61 years (IQR: 54-68 years); grade 1: 41%; grade 2: 41%; grade 3: 16%; unknown grade: 1%; tumor size (<1.5 cm: 67%, ≥1.5 cm: 33%); invasive ductal carcinoma: 82%; DCIS: 18%; nodal status (N0: 99%, number of positive nodes: 1%); sentinel lymph node biopsy: 74%; axillary lymph node dissection: 26%; unknown nodal assessment: 0%; estrogen receptor positive: 89%; HER2 positive: 5%; lymphovascular invasion: 6%; systemic therapy (none: 36%, endocrine: 58%, chemotherapy: 13%).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Rodrıguez, 2013[25, 26]	Noninferiority RCT in Spain, 2007 to 2013	APBI (3DCRT)	Inclusion: Patients with invasive ductal carcinoma; age ≥ 60 years; unifocal tumor; primary tumor size ≤ 30 mm (pT2); cN0, pN0 axillary status; and histologic grade 2 or less. Exclusion: Patients with bilateral breast carcinoma; prior unilateral or contralateral breast cancer; concomitant or other previous malignancies; pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; presence of an extensive intraductal component; excision with microscopically positive or close (≤3 mm) surgical margins; multicentric disease; node positive disease; concomitant or neoadjuvant chemotherapy; and postsurgical hematoma >2 cm, or seroma fluid that required multiple aspirations.	Median 10.3	51 patients aged 67.1 ± 6.1 years; tumor size: 1.04 ± 0.59 cm; estrogen receptor positive: 88.2%; progesterone receptor positive: 100%; HER2 positive: 1.9%; systemic therapy (endocrine: 98%, chemotherapy: 2%).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Rodrıguez, 2013[25, 26] (continued)	Noninferiority RCT in Spain, 2007 to 2013	WBI	Inclusion: Patients with invasive ductal carcinoma; age ≥ 60 years; unifocal tumor; primary tumor size ≤ 30 mm (pT2); cN0, pN0 axillary status; and histologic grade 2 or less. Exclusion: Patients with bilateral breast carcinoma; prior unilateral or contralateral breast cancer; concomitant or other previous malignancies; pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; presence of an extensive intraductal component; excision with microscopically positive or close (≤3 mm) surgical margins; multicentric disease; node positive disease; concomitant or neoadjuvant chemotherapy; and postsurgical hematoma >2 cm, or seroma fluid that required multiple aspirations.	Median 10.3	51 patients aged 70.1 ± 5.2 years; tumor size: 1.1 ± 0.58 cm; estrogen receptor positive: 84.3%; progesterone receptor positive: 98%; HER2 positive: 0%; systemic therapy (endocrine: 100%, chemotherapy: 3.9%).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Song, 2021[27]	Equivalence RCT in China, 06/2017 to 01/2019	APBI (3DCRT)	Inclusion: Patients age 45-75 years; life expectancy > 5 years; presence of histologically confirmed invasive ductal carcinoma (grade 1-2), mucinous carcinoma, papillary carcinoma, or tubular carcinoma with the maximum tumor diameter being ≤3.0 cm; or histologically confirmed ductal carcinoma in situ (low medium grade) with the maximum tumor diameter being ≤2.5 cm; pN0 (for patients with invasive carcinoma, either an axillary dissection with minimum of six nodes in the specimen or a negative sentinel node was required); presence of a unifocal tumor (confirmed by MRI); negative lymphovascular invasion; positive estrogen receptor or progesterone receptor status; negative resection margins of ≥2 mm; surgical clips placed in the tumor bed; and enrollment date <12 weeks after breast-conserving surgery <8 weeks after adjuvant chemotherapy. Exclusion: Presence of disease classified as stage II-IV per the 7th edition of the American Joint Committee on Cancer; invasive micropapillary carcinoma, lobular carcinoma in situ, invasive lobular carcinoma, or Paget's disease alone; previous oncoplastic surgery of the affected breast; neoadjuvant chemotherapy or hormonal therapy; presence of simultaneous contralateral breast cancer; previous ipsilateral breast or thorax irradiation; or active collagen vascular disease.	Median 2.2	70 patients aged 54 years (Range: 45-69 years); Asian: 100%; postmenopausal: 59.3%; Nodal status (N0: 100%); Lymphovascular invasion: 0%; %; HER2 positive: 6.8%; Prior chemotherapy: 0%; systemic therapy (endocrine: 100%, chemotherapy: 19.7%); other treatments: Trastuzumab: 5.1%; Unifocal: 100%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Song, 2021[27] (continued)	Equivalence RCT in China, 06/2017 to 01/2019	WBI	Inclusion: Patients age 45-75 years; life expectancy > 5 years; presence of histologically confirmed invasive ductal carcinoma (grade 1-2), mucinous carcinoma, papillary carcinoma, or tubular carcinoma with the maximum tumor diameter being ≤3.0 cm; or histologically confirmed ductal carcinoma in situ (low medium grade) with the maximum tumor diameter being ≤2.5 cm; pN0 (for patients with invasive carcinoma, either an axillary dissection with minimum of six nodes in the specimen or a negative sentinel node was required); presence of a unifocal tumor (confirmed by MRI); negative lymphovascular invasion; positive estrogen receptor or progesterone receptor status; negative resection margins of ≥2 mm; surgical clips placed in the tumor bed; and enrollment date <12 weeks after breast-conserving surgery <8 weeks after adjuvant chemotherapy. Exclusion: Presence of disease classified as stage II-IV per the 7th edition of the American Joint Committee on Cancer; invasive micropapillary carcinoma, lobular carcinoma in situ, invasive lobular carcinoma, or Paget's disease alone; previous oncoplastic surgery of the affected breast; neoadjuvant chemotherapy or hormonal therapy; presence of simultaneous contralateral breast cancer; previous ipsilateral breast or thorax irradiation; or active collagen vascular disease.	Median 2.2	70 patients aged 53.5 years (Range: 46-71 years); Asian: 100%; postmenopausal: 66.1%; Nodal status (N0: 100%); Lymphovascular invasion: 0%; %; HER2 positive: 7.1%; Prior chemotherapy: 0%; systemic therapy (endocrine: 100%, chemotherapy: 23.2%); other treatments: Trastuzumab: 7.1%; Unifocal: 100%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
TARGIT-A,[28-37] NCT00983684/ISRCTN34086741	Noninferiority RCT in the United Kingdom, Australia, Italy, Germany, the United States of America, Poland, Denmark, Canada, Switzerland, Norway, France, 03/2000 to 06/2012	APBI (IORT)	Inclusion: Patients aged ≥ 45 years with operable invasive breast cancer [tumor, nodes, metastasis (TNM) – T1 and small T2 ≤ 3.5 cm, N0–1, M0], confirmed by cytological or histological examination, who were suitable for breast-conserving surgery; tumor needed to be clinically suitable for breast conservation on conventional imaging; MRI scan was not required; individual centers could restrict entry to a more exactly defined subset of patients, in which case only patients with these characteristics could be entered by that particular center (for example, centers could at the outset decide to recruit only women aged > 50 years or even only women aged > 65 years); patients needed to be available for regular followup (according to local policies) for at least 10 years.	Median 9	1,721 patients aged (≤ 50 years: 9%, 51-60 years: 31%, 61-70 years: 45%, >70 years: 15%); grade 1: 35%; grade 2: 50%; grade 3: 15%; unknown grade: 11%; tumor size (≤ 1 cm: 39%, 1.1-2 cm: 48%, >2 cm: 12%); nodal status (N0: 83%, NX/unknown: 9%, 1-3 positive nodes: 14%, > 3 positive nodes: 3%); estrogen receptor positive: 92%; progesterone receptor positive: 81%; HER2 positive: 11%; lymphovascular invasion: 13%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
TARGIT-A,[28-37] NCT00983684/ISRCTN34086741 (continued)	Noninferiority RCT in the United Kingdom, Australia, Italy, Germany, the United States of America, Poland, Denmark, Canada, Switzerland, Norway, France, 03/2000 to 06/2012	APBI (IORT)	Exclusion: Patients with > one obvious cancer in the same breast as diagnosed by clinical examination, mammography or ultrasonography (MRI not required); bilateral breast cancer at the time of diagnosis; ipsilateral breast had a previous cancer and/or irradiation; patients known to have *BRCA* gene mutations but testing for gene mutations was not required; lobular cancer or extensive intraductal component (EIC) (in EIC ≥ 25% of the tumor is intraductal) on core biopsy or initial pathology (if performed); patients undergoing primary medical treatment (hormones or chemotherapy) as initial treatment with neoadjuvant intent of reducing tumor size; patients presenting with gross nodal disease, considered to be clinically malignant or proven cytologically or by scanning; patients with any severe concomitant disease that may limit their life expectancy; previous history of malignant disease with a relapse-free survival at 10 years of ≥ 90%; any factor included as an exclusion criterion in the local Centre's treatment policy; and no more than 30 days elapsed between last breast cancer surgery (not axillary) and entry into the trial for patients in the post pathology stratum.	Median 9	1,721 patients aged (≤ 50 years: 9%, 51-60 years: 31%, 61-70 years: 45%, >70 years: 15%); grade 1: 35%; grade 2: 50%; grade 3: 15%; unknown grade: 11%; tumor size (≤ 1 cm: 39%, 1.1-2 cm: 48%, >2 cm: 12%); nodal status (N0: 83%, NX/unknown: 9%, 1-3 positive nodes: 14%, > 3 positive nodes: 3%); estrogen receptor positive: 92%; progesterone receptor positive: 81%; HER2 positive: 11%; lymphovascular invasion: 13%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
TARGIT-A,[28-37] NCT00983684/ISRCTN34086741 (continued)	Noninferiority RCT in the United Kingdom, Australia, Italy, Germany, the United States of America, Poland, Denmark, Canada, Switzerland, Norway, France, 03/2000 to 06/2012	WBI	Inclusion: Aged ≥ 45 years with operable invasive breast cancer [tumor, nodes, metastasis (TNM) – T1 and small T2 ≤ 3.5 cm, N0–1, M0], confirmed by cytological or histological examination, who were suitable for breast-conserving surgery; tumor needed to be clinically suitable for breast conservation on conventional imaging; MRI scan was not required; individual centers could restrict entry to a more exactly defined subset of patients, in which case only patients with these characteristics could be entered by that particular center (for example, centers could at the outset decide to recruit only women aged > 50 years or even only women aged > 65 years); patients needed to be available for regular followup (according to local policies) for at least 10 years.	Median 9	1,730 patients aged (≤ 50 years: 7%, 51-60 years: 32%, 61-70 years: 47%, >70: 15%); grade 1: 37%; grade 2: 48%; grade 3: 15%; unknown grade: 13%; tumor size (≤ 1 cm: 39%, 1.1-2 cm: 48%, >2 cm: 14%); nodal status (N0: 85%, NX/unknown: 11%, 1-3 positive nodes: 14%, > 3 positive nodes: 2%); estrogen receptor positive: 94%; progesterone receptor positive: 82%; HER2 positive: 12%; lymphovascular invasion: 12%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
TARGIT-A,[28-37] NCT00983684/ISRCTN34086741 (continued)	Noninferiority RCT in the United Kingdom, Australia, Italy, Germany, the United States of America, Poland, Denmark, Canada, Switzerland, Norway, France, 03/2000 to 06/2012	WBI	Exclusion: > one obvious cancer in the same breast as diagnosed by clinical examination, mammography or ultrasonography (MRI not required); bilateral breast cancer at the time of diagnosis; ipsilateral breast had a previous cancer and/or irradiation; patients known to have *BRCA* gene mutations but testing for gene mutations was not required; lobular cancer or extensive intraductal component (EIC) (in EIC ≥ 25% of the tumor is intraductal) on core biopsy or initial pathology (if performed); patients undergoing primary medical treatment (hormones or chemotherapy) as initial treatment with neoadjuvant intent of reducing tumor size; patients presenting with gross nodal disease, considered to be clinically malignant or proven cytologically or by scanning; patients with any severe concomitant disease that may limit their life expectancy; previous history of malignant disease with a relapse-free survival at 10 years of ≥ 90%; any factor included as an exclusion criterion in the local Centre's treatment policy; and no more than 30 days elapsed between last breast cancer surgery (not axillary) and entry into the trial for patients in the post pathology stratum.	Median 9	1,730 patients aged (≤ 50: 7%, 51-60: 32%, 61-70: 47%, >70: 15%); grade 1: 37%; grade 2: 48%; grade 3: 15%; unknown grade: 13%; tumor size (≤ 1 cm: 39%, 1.1-2 cm: 48%, >2 cm: 14%); nodal status (N0: 85%, NX/unknown: 11%, 1-3 positive nodes: 14%, > 3 positive nodes: 2%); estrogen receptor positive: 94%; progesterone receptor positive: 82%; HER2 positive: 12%; lymphovascular invasion: 12%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Yadav, 2020[38]	Noninferiority RCT in India, 06/2011 to 12/2015	APBI (3DCRT)	Inclusion: Patients aged >35 years; invasive ductal carcinoma; unifocal tumor; primary tumor ≤4 cm (pT2); cN0, pN0-1 axillary nodes; and any histologic grade. Exclusion: Patients with previous ipsilateral or contralateral breast cancer; bilateral breast cancer; synchronous or other prior malignancies; lobular histology (in situ or invasive); presence of an extensive intraductal component; microscopically positive or close (2 mm) surgical margins; multicentric disease; concurrent or neoadjuvant chemotherapy; and seroma collection that required repeated aspirations.	Median 5	65 patients aged 50 ± 10.75 years; grade 1: 22%; grade 2: 57%; grade 3: 22%; nodal status (N0: 88%, N1: 11%, N2: 2%); estrogen receptor positive: 69%; progesterone receptor positive: 62%; HER2 positive: 12%; lymphovascular invasion: 14%; systemic therapy (endocrine: 75%, chemotherapy: 54%), other treatments: Trastuzumab: 4.6%; unifocal: 100%; positive margin: 8%.
	Noninferiority RCT in India, 06/2011 to 12/2015	WBI	Inclusion: Patients aged >35 years; invasive ductal carcinoma; unifocal tumor; primary tumor ≤4 cm (pT2); cN0, pN0-1 axillary nodes; and any histologic grade. Exclusion: Patients with previous ipsilateral or contralateral breast cancer; bilateral breast cancer; synchronous or other prior malignancies; lobular histology (in situ or invasive); presence of an extensive intraductal component; microscopically positive or close (2 mm) surgical margins; multicentric disease; concurrent or neoadjuvant chemotherapy; and seroma collection that required repeated aspirations.	Median 5	67 patients aged 50 ± 10 years; grade 1: 18%; grade 2: 58%; grade 3: 24%; nodal status (N0: 87%, N1: 12%, N2: 1%); estrogen receptor positive: 68%; progesterone receptor positive: 62%; HER2 positive: 10%; lymphovascular invasion: 18%; systemic therapy (endocrine: 72%, chemotherapy: 76%), other treatments (Trastuzumab: 4.5%; unifocal: 100%; positive margin: 10%).

Abbreviations: ± = standard deviation; 2DRT = 2-dimensional radiotherapy; 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; ASTRO = American Society for Radiation Oncology; cm = centimeter; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component; ER = estrogen

receptor; HER2 = Human Epidermal Growth Factor Receptor-2; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; IQR = interquartile range; KQ = Key Question; mm = millimeter; MRI = magnetic resonance imaging; NR = not reported; PBI = partial breast irradiation; PR = progesterone receptor; RCT= randomized clinica trial; WBI = whole breast irradiation

Table D.2. Characteristics of included studies. KQ 2: Comparisons of different PBI modalities

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Budapest,[2] 2007,[1,3] 2013,[4] 2021[5]	Noninferiority RCT in Hungary 07/1998 to 05/2004	APBI (multi-catheter interstitial brachytherapy or APBI (3DCRT)	Inclusion: Patients with wide excision with microscopically negative surgical margins; unifocal tumor; primary tumor size ≤20 mm (pT1); cN0, pN0, or pN1mi (single nodal micrometastasis > 0.2mm and ≤ 2.0 mm) axillary status; and histologic grade 2 or less. Exclusion: Patients aged ≤ 40 years; bilateral breast carcinoma; prior uni- or contralateral breast cancer; concomitant or previous other malignancies (except basal cell carcinoma of the skin); pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; or the presence of an extensive intraductal component.	Median 17	128 patients aged 59 years (Range: 30-84 years); tumor size: 1.3 cm (<1.5 cm: 36.5%, 1.1-2 cm: 63.3%); nodal status (N0: 94.5%, N1; 2.3%, NX/unknown: 3.2%); estrogen receptor positive: 90.6%; progesterone receptor positive: 81.2%; lymphovascular invasion: 2.3%; unifocal: 100%; surgical margins (<2 mm: 0%; 2-10 mm: 58.6%; >10 mm: 37.5%).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Budapest,[2] 2007,[1, 3] 2013,[4] 2021[5] (continued)	Noninferiority RCT in Hungary 07/1998 to 05/2004	WBI	Inclusion: Patients with wide excision with microscopically negative surgical margins; unifocal tumor; primary tumor size ≤20 mm (pT1); cN0, pN0, or pN1mi (single nodal micrometastasis > 0.2mm and ≤ 2.0 mm) axillary status; and histologic grade 2 or less. Exclusion: Patients aged ≤ 40 years; bilateral breast carcinoma; prior uni- or contralateral breast cancer; concomitant or previous other malignancies (except basal cell carcinoma of the skin); pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; or the presence of an extensive intraductal component.	Median 17	130 patients aged 58 years (Range: 31-80 years); tumor size: 1.3 cm (<1.5 cm: 29.2%, 1.1-2 cm: 70.8%); nodal status (N0: 94.6%, N1; 4.6%, NX/unknown: 0.8%); estrogen receptor positive: 86.9%; progesterone receptor positive: 78.4%; lymphovascular invasion: 4.6%; unifocal: 100%; surgical margins (<2 mm: 0.8%; 2-10 mm: 58.5%; >10 mm: 26.1%).
Bush, 2011,[39] 2014,[40] NCT00614172	Single-arm observational study in the United States of America	APBI (proton radiation therapy)	Inclusion: Patients had biopsy-proven invasive carcinoma of the breast; had primary tumor that were ≤ 3 cm in greatest dimension. Exclusion: Patients with invasive lobular carcinoma and extensive ductal carcinoma in situ.	Median 5	100 patients aged 63 years (Range: 41-83 years); postmenopausal: 45%; tumor size: 1.3 cm (Range: 0.3-2.8); estrogen receptor positive: 88%; progesterone receptor positive: 70%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Galland-Girodet, 2014,[41] NCT00694577	Comparative observational study in the United States of America, 10/2003 to 04/2006	APBI (3DCRT)	Inclusion: Patients aged 18 years or older with pT1N0M0 invasive breast carcinoma. Exclusion: Patients with the presence of lymphovascular or blood vessel invasion; extensive intraductal component; invasive lobular carcinoma or mixed ductal-lobular histology; test results showing a mutation known to predispose to breast cancer development, including *BRCA1* or *BRCA2*; previous cosmetic or reconstructive breast surgery; psychiatric illness preventing the patient from giving informed consent; medical conditions such as uncontrolled infection (including human immunodeficiency virus), uncontrolled diabetes mellitus, or connective tissue diseases; pregnancy; or a currently active second malignancy other than nonmelanoma skin cancers.	Median 6.9	79 patients aged 60 years; grade 1: 36%; grade 2: 36%; grade 3: 7%; tumor size: 0.9 cm; invasive ductal carcinoma: 91%; tubular: 4%; mucinous: 4%; IDC with DCIS: 1%; estrogen receptor positive: 90%; progesterone receptor positive: 80%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Galland-Girodet, 2014,[41] NCT00694577 (continued)	Comparative observational study in the United States of America 10/2003 to 04/2006	APBI (proton radiation therapy)	Inclusion: Patients aged 18 years or older with pT1N0M0 invasive breast carcinoma. Exclusion: Patients with the presence of lymphovascular or blood vessel invasion; extensive intraductal component; invasive lobular carcinoma or mixed ductal-lobular histology; test results showing a mutation known to predispose to breast cancer development, including *BRCA1* or *BRCA2*; previous cosmetic or reconstructive breast surgery; psychiatric illness preventing the patient from giving informed consent; medical conditions such as uncontrolled infection (including human immunodeficiency virus), uncontrolled diabetes mellitus, or connective tissue diseases; pregnancy; or a currently active second malignancy other than nonmelanoma skin cancers.	Median 6.9	19 patients aged 61 years; grade 1: 10%; grade 2: 6%; grade 3: 3%; tumor size: 0.8 cm; invasive ductal carcinoma: 89%; tubular: 11%; mucinous: 0%; IDC with DCIS: 0%; estrogen receptor positive: 84%; progesterone receptor positive: 78%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Jacobs, 2018,[42] 2019,[43] 2021,[44] 2022[45]	Comparative observational study in the Netherlands, 2011 to 11/2016	APBI (IORT)	Inclusion: Patients aged 60 years or older; with invasive or in situ breast tumors of ≤ 30 mm (cT1 and any hormonal receptor status or cT2 and ER/PR positive and HER2 negative); and clinical N0 status eligible for breast conserving therapy and sentinel node procedure. Exclusion: Patients with multicentric or multifocal tumors; extensive intraductal carcinoma or lymphovascular invasion; positive surgical margins; > pN1a after sentinel node procedure; neoadjuvant chemotherapy; previous malignancy in the past 5 years; or previous radiotherapy on the ipsilateral breast.	Median 5.2	316 patients aged (60-69 years: 62%, ≥ 70 years: 38%); Invasive grade (grade 1: 31.4%; grade 2: 44.9%; grade 3: 23.7%, unknown: 0.02%); DCIS grade(grade 1: 27.8%, grade 2: 44.3%, grade 3: 27.8%, unknown: 1.3%); Tumor size (≤ 2 cm: 68%, >2 cm: 32%); DCIS: 92.1%; histologic subtype (Luminal A: 72.7%, Luminal B Her 2 negative: 15.3%, Luminal B Her 2 positive: 5.1%, HER2 positive: 1.1%, Triple negative: 5.8%); nodal status (N0: 86.5%, pNmi: 12.8%, NX/unknown: 0.7%); ASTRO risk (suitable: 55%, cautionary or unsuitable: 45 %); estrogen receptor positive: 92.9%; HER2 positive: 6.2%; systemic therapy (none: 55.6%, endocrine: 34.9%, chemotherapy: 2.6%, endocrine and chemotherapy: 6.9%, unknown: 0.3); Unifocal: 100%; margin status-invasive (positive: 1.5%, < 2 mm: 6.2%, ≥ 2 mm : 92.3%); margin status-DCIS (positive: 7.7%, < 2 mm: 18.3%, ≥ 2 mm : 74%).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Jacobs, 2018,[42] 2019,[43] 2021,[44] 2022,[45] (continued)	Comparative observational study in the Netherlands, 2011 to 11/2016	APBI (3DCRT or IMRT)	Inclusion: Patients aged 60 years or older; with invasive or in situ breast tumors of ≤ 30 mm (cT1 and any hormonal receptor status or cT2 and ER/PR positive and HER2 negative); and clinical N0 status eligible for breast conserving therapy and sentinel node procedure. Exclusion: Patients with multicentric or multifocal tumors; extensive intraductal carcinoma or lymphovascular invasion; positive surgical margins; > pN1a after sentinel node procedure; neoadjuvant chemotherapy; previous malignancy in the past 5 years; or previous radiotherapy on the ipsilateral breast.	Median 5	301 patients aged (60-69 years: 58.6%, ≥ 70 years: 41.4%); Invasive grade (grade 1: 30.7%; grade 2: 52.8%; grade 3: 16.5%. unknown: 2.03%); DCIS grade(grade 1: 20.1%, grade 2: 50.7%, grade 3: 29.2%, unknown: 2.7%); Tumor size (≤ 2 cm: 91%, >2 cm: 9%); DCIS: 88.1%; Other histologic subtype (Luminal A: 80%, Luminal B Her 2 negative: 10.2%, Luminal B Her 2 positive: 4.1%, Her 2 positive: 1.6%, Triple negative: 4.1%); nodal status (N0: 83.1%, pNmi: 14.2%, NX/unknown: 2.7%); ASTRO risk (suitable: 39%, cautionary or unsuitable: 61 %); estrogen receptor positive: 93.%; HER2 positive: 5.7%; systemic therapy (none: 53.9%, endocrine: 34.5%, chemotherapy: 2.7%, endocrine and chemotherapy: 8.9%, unknown: 0.7); Unifocal: 100%; margin status-invasive (positive: 8.1%,< 2 mm: 17.4%, ≥ 2 mm : 74.4%); margin status-DCIS (positive: 16.2%, < 2 mm: 22.1%, ≥ 2 mm : 61.7%). .

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Leonard, 2021[46]	Equivalence RCT in the United States of America, 07/2009 to 04/2015	APBI (3DCRT)	Inclusion: Patients with pathological stage ≤ T2 N0 breast cancer, ≥40 years of age, ≤3 cm focus maximum diameter of invasive/intraductal carcinoma, and ≥2 mm margins. Exclusion: Patients with gross multifocal disease.	Median 3	328 Patients aged 63.1±10.2; African American: 1.2%; White: 94.2%; Asian: 0.6%; Hispanic: 2.7%; other race/ethnicity: 1.3%; Tumor size: 1.08±0.61; DCIS; 21.7%; invasive ductal carcinoma: 70.7%; invasive lobular carcinoma: 7%; other histologic subtype: 0.6%; nodal status (N0: 100%); estrogen receptor positive: 92.1%; HER2 positive: 5.5%.
	Equivalence RCT in the United States of America, 07/2009 to 04/2015	APBI (IMRT)	Inclusion: Patients with pathological stage ≤ T2 N0 breast cancer, ≥40 years of age, ≤3 cm focus maximum diameter of invasive/intraductal carcinoma, and ≥2 mm margins. Exclusion: Patients with gross multifocal disease.	Median 3	328 Patients aged 61±9.6; African American: 0.6%; White: 94.5%; Asian: 1.2%; Hispanic: 3.1%; other race/ethnicity: 0.6%; Tumor size: 1.09±0.56; DCIS; 13.7%; invasive ductal carcinoma: 79.3%; invasive lobular carcinoma: 6.4%; other histologic subtype: 0.6%; nodal status (N0: 100%); estrogen receptor positive: 94.5%; HER2 positive: 5.8%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Meszaros, 2020,[47] NCT02003560	Comparative observational study in Hungary, 12/2006 to 03/2014	APBI (3DCRT)	Inclusion: Patients with low-risk, stage I–II breast cancer who underwent breast-conserving surgery followed by postoperative APBI and met all of the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status = 0–1; life expectancy ≥ 5 years; unifocal invasive tumor; primary tumor size at final pathology ≤ 30 mm; microscopically clear inked surgical margins of at least 2 mm; pN0 axillary status (proved by negative sentinel lymph nodes retrieved by axillary dissection); and excision cavity visible on planning computed tomography (CT) marked with titanium clips; written informed consent. Exclusion: Patients with multifocal tumor; pure ductal or lobular carcinoma in situ (pTis); invasive tumors with the presence of an extensive intraductal component (EIC); lymphovascular invasion (LVI); Paget disease of the nipple; bilateral breast cancer; pregnancy or lactation; other illness accompanied by increased radiosensitivity (e.g. collagen vascular disease); prior history of breast cancer; prior history of other malignant disease within 5 years; psychiatric disorder preventing the cooperation of the patient.	Median 7.5	44 patients aged 62.6 years (Range: 47-77 years); cup size (A: 2.3%, B: 54.5%, C: 31.8%, ≥ D: 11.4%); postmenopausal: 90.9%; grade 1: 56.8%; grade 2: 29.6%; grade 3: 13.6%; tumor size: 1.2 cm (≤1 cm: 38.6%, 1.1-2 cm: 52.3%, > 2 cm: 9.1%); invasive ductal carcinoma: 91%, invasive lobular carcinoma: 4.5%; papillary: 4.5%; sentinel lymph node biopsy: 90.9%; axillary lymph node dissection: 9.1%; combined ER/PR positive: 93.1%; systemic therapy (endocrine: 95.5%, chemotherapy: 6.8%); surgical margin (≥2-<5 mm: 30%, ≥5-<10 mm: 33.3%, ≥10 mm: 36.7%).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Meszaros, 2020,[47] NCT02003560 (continued)	Comparative observational study in Hungary, 12/2006 to 03/2014	APBI (IMRT)	Inclusion: Patients with low-risk, stage I–II breast cancer who underwent breast-conserving surgery followed by postoperative APBI and met all of the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status = 0–1; life expectancy ≥ 5 years; unifocal invasive tumor; primary tumor size at final pathology ≤ 30 mm; microscopically clear inked surgical margins of at least 2 mm; pN0 axillary status (proved by negative sentinel lymph nodes retrieved by axillary dissection); and excision cavity visible on planning computed tomography (CT) marked with titanium clips; written informed consent. Exclusion: Patients with multifocal tumor; pure ductal or lobular carcinoma in situ (pTis); invasive tumors with the presence of an extensive intraductal component (EIC); lymphovascular invasion (LVI); Paget disease of the nipple; bilateral breast cancer; pregnancy or lactation; other illness accompanied by increased radiosensitivity (e.g. collagen vascular disease); prior history of breast cancer; prior history of other malignant disease within 5 years; psychiatric disorder preventing the cooperation of the patient.	Median 7.5	60 patients aged 61 years (Range: 40-74 years); cup size (A: 1.7%, B: 21.6%, C: 55%, ≥ D: 21.6%); postmenopausal: 91.6%; grade 1: 70%; grade 2: 28.3%; grade 3: 1.7%; tumor size: 1.15 cm (≤1 cm: 43.3%, 1.1-2 cm: 55%, > 2 cm: 1.7%); invasive ductal carcinoma: 93.3%, invasive lobular carcinoma: 1.7%; tubular: 3.3%; mucinous: 1.7%; sentinel lymph node biopsy: 96.7%; axillary lymph node dissection: 3.3%; combined ER/PR positive: 81.6%; systemic therapy (endocrine: 91.7%, chemotherapy: 1.7%); surgical margin (≥2-<5 mm: 29.6%, ≥5-<10 mm: 63.6%, ≥10 mm: 6.8%).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Mutter, 2019[48]	Single-arm observational study in the United States of America, 12/2015 to 11/2017	APBI (proton radiation therapy)	Inclusion: Patients aged 50 years or older; pathologic tumor size ≤2.5 cm; estrogen receptor-positive invasive breast cancer confirmed lymph node negative; or pure DCIS. Exclusion: NR	Median 1	76 patients aged 67 years (Range: 51-81 years); grade 1: 40%; grade 2: 51%; grade 3: 8%; tumor size (≤1 cm: 33%, 1.1-2 cm: 62%, > 2 cm: 5%); invasive ductal carcinoma: 96%, invasive lobular carcinoma: 1%; DCIS: 20%; other histologic subtype: 3%; estrogen receptor positive: 97%; HER2 positive: 3%; systemic therapy (endocrine: 67%, chemotherapy: 1%).
Pasalic, 2021,[49] NCT01245712	Single-arm observational study in the United States of America, 2010 to 2019	APBI (proton radiation therapy)	Inclusion: Women with ductal carcinoma in situ (any grade) or early-stage invasive breast carcinoma with negative margins of ≥ 3 cm who were referred after a segmental mastectomy. Exclusion: Men had tumors > 3.0 cm; persistently positive margins; multicentric carcinoma in more than 1 quadrant or separated by 4 cm or more; received treatment requiring regional nodal irradiation; received prior radiation therapy to the index breast; were pregnant; or had a diagnosis of collagen vascular disease.	Median 2	100 patients aged 67 years (Range: 62-71 years); African American: 7%; White: 88%; Hispanic: 5%; invasive ductal carcinoma: 65%, invasive lobular carcinoma: 10%; DCIS: 23%; mucinous: 1%; papillary: 1%; nodal status (N0: 83%, NX/unknown: 17%); estrogen receptor positive: 94%; HER2 positive: 10%; systemic therapy (endocrine: 63%, chemotherapy: 5%, endocrine and chemotherapy: 3%).

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Shah, 2004[50]	Comparative observational study in the United States of America, 06/1997 to 09/2003	APBI (multi-catheter interstitial brachytherapy)	Inclusion: Patients without positive lymph node; tumors were required to measure < 2 cm in greatest dimension; the volume of the lumpectomy cavity had to be consistent with the manufacturer's recommendations with respect to the dimension of the balloon selected, and a distance > 5mm was required between the balloon surface and the skin. Exclusion: Patients with tumor histologic features with invasive or in situ lobular carcinoma or pure ductal carcinoma in situ; skin involvement; a breast unsatisfactory for brachytherapy (defined as having < 1 cm thickness of breast tissue within the entire implant volume, as measured from the skin to the pectoralis fascia or the subareolar position of the lumpectomy cavity); and last breast surgery > 8 weeks before planned interstitial brachytherapy or MammoSite brachytherapy.	Median 5.1	75 patients aged 63.5 ± 10.7 years; grade 1: 51.9%; grade 2: 47.1%; tumor size: 1.3 cm (Range: 0.3-4 cm); invasive ductal carcinoma: 100%; nodal status (N0: 100%); sentinel lymph node biopsy: 55%; axillary lymph node dissection: 44%; estrogen receptor positive: 85%; systemic therapy (endocrine: 68%, chemotherapy: 18.7%); unifocal: 100%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Shah, 2004[50] (continued)	Comparative observational study in the United States of America, 06/1997 to 09/2003	APBI (single-entry catheter brachytherapy)	Inclusion: Patients without positive lymph node; tumors were required to measure < 2 cm in greatest dimension; the volume of the lumpectomy cavity had to be consistent with the manufacturer's recommendations with respect to the dimension of the balloon selected, and a distance > 5 mm was required between the balloon surface and the skin. Exclusion: Patients with tumor histologic features with invasive or in situ lobular carcinoma or pure ductal carcinoma in situ; skin involvement; a breast unsatisfactory for brachytherapy (defined as having < 1 cm thickness of breast tissue within the entire implant volume, as measured from the skin to the pectoralis fascia or the subareolar position of the lumpectomy cavity); and last breast surgery > 8 weeks before planned interstitial brachytherapy or MammoSite brachytherapy.	Median 5.1	28 patients aged 62 ± 10 years; grade 1: 51%; grade 2: 49%; tumor size: 1.1 cm (Range 0.3-2 cm); invasive ductal carcinoma: 100%; nodal status (N0: 100%); sentinel lymph node biopsy: 89%; axillary lymph node dissection: 7%; estrogen receptor positive: 100%; systemic therapy (endocrine: 89.3%, chemotherapy: 0%); unifocal: 100%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Shah, 2012[51]	Comparative observational study in the United States of America, 04/1993 to 11/2010	APBI (multi-catheter interstitial brachytherapy)	Inclusion: Patients having infiltrating ductal carcinomas less than 3.0 cm in diameter; having negative surgical margins (≥ 2 mm); being over 40 years of age; and having negative lymph nodes. Exclusion: Patients with an extensive intraductal component; infiltrating lobular histology; ductal carcinoma in situ; or clinically significant areas of lobular carcinoma in situ.	Mean 3	3 patients aged 58 years (Range: 48-65 years); tumor size: 0.67 cm (Range 0.5-0.9 cm); estrogen receptor positive: 100%; progesterone receptor positive: 100%; systemic therapy (endocrine: 100%, chemotherapy: 0%); positive margin status: 0%; free surgical margin < 2 mm: 67%.
	Comparative observational study in the United States of America, 04/1993 to 11/2010	APBI (single-entry catheter brachytherapy)	Inclusion: Patients having infiltrating ductal carcinomas less than 3.0 cm in diameter; having negative surgical margins (≥ 2 mm); being over 40 years of age; and having negative lymph nodes. Exclusion: Patients with an extensive intraductal component; infiltrating lobular histology; ductal carcinoma in situ; or clinically significant areas of lobular carcinoma in situ.	Mean 3	53 patients aged 62.3 years (Range: 48-84 years); tumor size: 0.79 cm (Range 0.1-2.5 cm); estrogen receptor positive: 88%; progesterone receptor positive: 79%; systemic therapy (endocrine: 47%, chemotherapy: 0%); positive margin status: 10%; free surgical margin < 2 mm: 34%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Shah, 2012[51] (continued)	Comparative observational study in the United States of America, 04/1993 to 11/2010	APBI (3DCRT)	Inclusion: Patients having infiltrating ductal carcinomas less than 3.0 cm in diameter; having negative surgical margins (≥ 2 mm); being over 40 years of age; and having negative lymph nodes. Exclusion: Patients with an extensive intraductal component; infiltrating lobular histology; ductal carcinoma in situ; or clinically significant areas of lobular carcinoma in situ.	Mean 3	43 patients aged 61.4 years (Range: 37-82 years); tumor size: 0.69 cm (Range 0.1-2.8 cm); estrogen receptor positive: 85%; progesterone receptor positive: 80%; systemic therapy (endocrine: 61%, chemotherapy: 0%); positive margin status: 8%; free surgical margin < 2 mm: 25%.
Stecklein, 2019[52]	Comparative observational study in the United States of America, 12/2008 to 08/2014	APBI (single-entry catheter brachytherapy)	Inclusion: Adults ≥ 50 years; pathologic diagnosis of invasive ductal or lobular carcinoma, and/or DCIS measuring ≤3.0 cm; clinically unifocal disease; margins ≥2.0 mm; pN0 (for patients with invasive disease); and willingness to sign a study-specific consent form. Exclusion: Patients who had lymphovascular space invasion; history of systemic lupus or scleroderma; prior breast or thoracic radiotherapy; prior ipsilateral breast cancer; clinically multifocal disease; or microscopic multifocality >3.0 cm.	Median 3.4	252 patients aged 61 years (Range: 50-86 years); African American: 9.1%; White: 81%; Asian: 1.6%; Hispanic: 6%; other race/ethnicity: 2.4%; cup size (A: 4.8%, B: 21%, C: 30.6%, ≥ D: 39.7%); ASTRO risk (suitable: 80.2%, cautionary: 19.8%); combined ER/PR positive: 90%; HER2 positive: 3.17%; systemic therapy (endocrine: 69.4%, chemotherapy: 6%); free surgical margin <3 mm: 6.5%.

Trial Acronym/Author, Year	Country, Study Design, Patient Enrollment Period	Intervention(s) and Comparison	Inclusion and Exclusion Criteria	Length of Followup (Years)	Patient Characteristics
Stecklein, 2019[52] (continued)	Comparative observational study in the United States of America, 12/2008 to 08/2014	APBI (3DCRT)	Inclusion: Adults ≥ 50 years; pathologic diagnosis of invasive ductal or lobular carcinoma, and/or DCIS measuring ≤3.0 cm; clinically unifocal disease; margins ≥2.0 mm; pN0 (for patients with invasive disease); and willingness to sign a study-specific consent form. Exclusion: Patients who had lymphovascular space invasion; history of systemic lupus or scleroderma; prior breast or thoracic radiotherapy; prior ipsilateral breast cancer; clinically multifocal disease; or microscopic multifocality >3.0 cm.	Median 3.4	29 patients aged 62 years (Range: 50-73 years); African American: 6.9%; White: 86.2%; Asian: 0%; Hispanic: 6.9%; other race/ethnicity: 0%; cup size (A: 3.4%, B: 10.3%, C: 24.1%, ≥ D: 17.2%); ASTRO risk (suitable: 79.3%, cautionary: 20.7%); combined ER/PR positive: 93.1%; HER2 positive: 6.9%; systemic therapy (endocrine: 62.1%, chemotherapy: 3.4%); free surgical margin <3 mm: 0%.

Abbreviations: ± = standard deviation; 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; ASTRO = American Society for Radiation Oncology; cm = centimeter; DCIS = ductal carcinoma in situ; ECOG = Eastern Cooperative Oncology Group; EIC = extensive intraductal component; ER = estrogen receptor; HER2 = Human Epidermal Growth Factor Receptor-2; IDC = intra-ductal carcinoma; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; LVI = lymphovascular invasion; mm = millimeter; NR = not reported; PBI = partial breast irradiation; PR = progesterone receptor; RCT= randomized clinica trial; WBI = whole breast irradiation

Appendix E. Characteristics of Interventions

Table E.1. Characteristics of interventions. KQ 1: PBI versus WBI

Trial Acronym/Author, Year, Study Design	Intervention(s) and Comparison	Dose and Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose)	Target Volumes	Planning Parameters
Budapest,[2] 2007,[1, 3] 2013,[4] 2021,[5] noninferiority RCT	APBI (multi-catheter interstitial brachytherapy)	36.4 Gy in 7 fractions, twice daily	PTV: 2 cm.	Brachytherapy Goals NR, V100, V150, Dose-non uniformity ratio reported Skin Max <60% Prescription
	APBI (3DCRT)	50 Gy in 25 fractions, once daily	PTV: 2 cm.	Brachytherapy Goals NR, V100, V150, Dose-non uniformity ratio reported Skin Max <60% Prescription
	WBI	50 Gy in 25 fractions, once daily	PTV: Whole breast.	NR
Dodwell, 2005,[6] RCT	Nonaccelerated PBI (3DCRT/2DRT, and electrons)	55 Gy in 20 fractions, once daily over 28 days	CTV: Defined clinically. PTV: Variable; not explicitly defined.	NR
	WBI	40 Gy in 15 fractions, once daily, over 21 days, with boost of 15 Gy in 5 fractions	CTV: Defined clinically by palpation of breast tissue. PTV: The clinical target volume plus an additional 1 cm expansion.	NR

Trial Acronym/Author, Year, Study Design	Intervention(s) and Comparison	Dose and Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose)	Target Volumes	Planning Parameters
ELIOT,[7, 8] NCT01849133, equivalence RCT	APBI (IORT)	21 Gy in one fraction, once	CTV: NR. PTV: NR.	Ipsilateral lung: Volume of lung receiving 50% of prescribed dose kept to <20% Heart: Volume of heart receiving 50% of the prescribed dose kept to <5%
	WBI	50 Gy in 25 fractions, with boost of 10 Gy in 5 fractions delivered using a direct external electron beam (all patients).	CTV and PTV: NR.	Ipsilateral lung: Volume of lung receiving 50% of prescribed dose kept to <20%. Heart: Volume of heart receiving 50% of the prescribed dose kept to <5%

Trial Acronym/Author, Year, Study Design	Intervention(s) and Comparison	Dose and Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose)	Target Volumes	Planning Parameters
Florence,[9-13] NCT02104895, equivalence RCT	APBI (IMRT)	30 Gy in 5 fractions, once every 2 days	CTV: 1 cm margin around surgical clips. PTV: 1 cm The PTV was allowed to extend 0.4 cm inside the ipsilateral lung and was limited to 0.3 cm from the skin.	Ipsilateral breast: Volume of breast receiving 50% of the prescribed dose kept to <50% (V15Gy <50%). Ipsilateral lung: Volume of lung receiving 10 Gy kept to <20% (V10Gy <20%). Heart: Volume of heart receiving 3 Gy kept to <10% (V3Gy <10%). PTV: 100% of PTV covered by 95% of the prescribed dose (V28.5 = 100%); maximal dose to PTV <105% (31.5 Gy); minimal dose to PTV 28 Gy. Homogeneity of the dose to the target was controlled by keeping the maximum dose within 31.5 Gy. Use of clips for localization: 100%. Image guidance: Positioning was imaged using orthogonal portal images or with cone-beam CT before each fraction
	WBI	50 Gy in 25 fractions, once daily followed by a boost to the tumor bed of 10 Gy in five fractions (all patients)	CTV and PTV: NR.	Use of clips for localization: 100%. Ipsilateral breast: Homogeneity of the dose to the target was controlled by keeping the maximum dose within 53.5 Gy. Ipsilateral lung: Volume of lung receiving 20 Gy kept <20%. Heart: Volume of heart receiving 20 Gy kept <5% of heart to receive <20 Gy.

Trial Acronym/Author, Year, Study Design	Intervention(s) and Comparison	Dose and Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose)	Target Volumes	Planning Parameters
GEC-ESTRO,[14-17] NCT00402519, noninferiority RCT	APBI (multi-catheter interstitial brachytherapy)	High dose rate brachytherapy: 32 Gy in 8 fractions or 30.3 Gy in 7 fractions, twice daily Pulsed-dose-rate brachytherapy: Total dose of 50 Gy with pulses of 0.60-0.80 Gy/hour (1 pulse/hour, 24 hours/day)	CTV: At least 2 cm, defined individually.	PTV: 100% of the prescribed dose to cover at least 90% of the target volume Skin: maximum dose <70% prescribed dose
	WBI	50 Gy (50-50.4 Gy) in 25-28 fractions, once daily, for 6-7 weeks + 10 Gy boost in 5 fractions (all patients)	CTV: NR.	PTV: Maximum dose < 115%
HYPAB,[18] RCT	APBI (IMRT)	30 Gy in 5 fractions of 6 Gy on alternate days	CTV: 1 cm. PTV: 0.5 cm.	Ipsilateral breast: Uninvolved breast (i.e. ipsilateral breast without PTV) volume receiving more than 15 Gy not exceeding 50% (V15Gy ≤ 50%). Ipsilateral lung: Volume receiving more than 10 Gy not exceeding 20% (V 10Gy ≤ 20%). Heart: Volume receiving more than 3 Gy not exceeding 10% (V3Gy ≤ 10%); acceptable for volume receiving more than 5 Gy not to exceed 10%. PTV: D98% > 95% and D2% < 107% for the high dose PTV Image guidance (cone beam CT): 100%. Use of clips for localization: 100%.

Trial Acronym/Author, Year, Study Design	Intervention(s) and Comparison	Dose and Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose)	Target Volumes	Planning Parameters
HYPAB,[18] RCT (continued)	WBI	40.5 Gy in 15 fractions, once daily, over 3 weeks + 48 Gy integrated boost (all patients)	CTV: Whole breast PTV: 0.5 cm, limited to 0.5 cm within the skin surface.	Ipsilateral lung: Volume receiving 20 Gy not to exceed 10% (V20 Gy≤ 10%); mean lung dose <10Gy. Heart: Volume of heart receiving 40 Gy not exceeding 3% and volume receiving 18 Gy not exceeding 5%; mean heart dose <4 Gy. PTV: D98% > 95% and D2% < 107% for the high dose PTV Image guidance (use of clips for localization): 100%.

Trial Acronym/Author, Year, Study Design	Intervention(s) and Comparison	Dose and Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose)	Target Volumes	Planning Parameters
NSABP B-39/RTOG 0413,[19] NCT00103181, equivalence RCT	APBI (single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, 3DCRT)	Brachytherapy: 34 Gy in 10 fractions, twice per day 3DCRT: 38.5 Gy in 10 fractions, twice per day	3DCRT: CTV: 1.5 cm, limited to 5 mm from skin surface and by the chest wall or pectoralis muscles PTV: 1 cm, limited to 0.5 cm from skin surface and by the chest wall or pectoralis muscles Single-entry catheter brachytherapy: CTV: uniform 1 cm expansion of the balloon/device, limited to 0.5 cm from skin surface and by the chest wall or pectoralis muscles PTV: same as CTV Multi-catheter interstitial brachytherapy: uniform expansion of the lumpectomy cavity by 1.5 cm, limited to 0.5 cm from skin and by the chest wall or pectoralis muscles PTV: same as CTV .	3DCRT: Ipsilateral breast: Volume of breast receiving 50% of prescribed dose kept to < 60%; volume of breast receiving prescription dose kept to <35% Ipsilateral lung: Volume of lung receiving 30% of the prescribed dose kept to <15% Heart: Right sided: volume of heart receiving 5% of the prescribed dose kept to <5%; left sided: volume of heart receiving 5% of the prescribed dose kept to <40%. PTV: 90% of the PTV volume covered by 90% of the prescription dose; maximum dose <120% Single-entry catheter brachytherapy and multi-catheter interstitial brachytherapy: Ipsilateral breast: Volume of breast receiving 50% of prescribed dose kept to < 60%, subtracting the balloon/device volume from the breast volume PTV: 90% of the PTV volume covered by 90% of the prescription dose Image guidance: Portal films or images of each beam and an orthogonal pair prior to initiation of treatment, and subsequent images obtained prior to fraction number 5. Additional images obtained at the investigator's discretion.

Trial Acronym/Author, Year, Study Design	Intervention(s) and Comparison	Dose and Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose)	Target Volumes	Planning Parameters
NSABP B-39/RTOG 0413,[19] NCT00103181, equivalence RCT (continued)	WBI	50 Gy in 25 fractions, 5 days per week Boost of 10-16.2 Gy (received by 80%)	CTV: NR PTV: NR	Ipsilateral lung: < 3 cm of lung tissue included within the tangent field.
UK IMPORT LOW,[20, 21] ISRCTN12852634, noninferiority RCT	Nonaccelerated PBI (3DCRT)	40 Gy in 15 fractions, once daily	CTV: 1.5 cm, 0.5 cm from skin surface and not extending beyond pectoral fascia posteriorly PTV: 1 cm, 0.5 cm from skin	PTV: ≥95% of volume should receive 95% of prescription dose.
	WBI	40 Gy in 15 fractions, once per day No boost.	CTV: Whole breast. PTV: NR.	PTV: ≥90% of volume should receive 95% of prescription dose. Ipsilateral lung: Maximum lung depth of tangent field not to exceed 2 cm

Trial Acronym/Author, Year, Study Design	Intervention(s) and Comparison	Dose and Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose)	Target Volumes	Planning Parameters
RAPID,[22-24] NCT00282035, noninferiority RCT	APBI (3DCRT or IMRT)	38.5 Gy in 10 fractions, twice per day over 5-8 days	CTV: 1 cm. PTV: 1 cm, 0.5 cm from skin and excluding chest wall and pectoralis major.	Ipsilateral breast: 0% to receive > 107%, < 25% to receive 95% and < 50% to receive > 50% of the prescription dose. Ipsilateral lung: <20% of the volume to receive 10% of the prescribed dose and <10% of the volume to receive 30% of the prescribed dose. Heart: Right sided: <5% of the volume to receive 5% of the prescribed dose; Left sided excluding lower inner quadrant cancers: <5% of the volume to receive 10% of the prescribed dose; Left sided with a lower inner quadrant cancer: <5% of the volume to receive <15% of the dose. PTV: Covered with 95-107% of the prescription dose. Image guidance: Portal images of each field or orthogonal images should be performed on at least two occasions within the first 2-3 days of treatment
	WBI	42.5 Gy in 16 fractions or 50 Gy in 25 fractions, once per day over 21 days Boost to the lumpectomy cavity: 10 Gy in 4-5 fractions (received by 21%).	CTV: Whole breast. PTV: NR	PTV: Treated uniformly from 95% to 107% of the prescription dose, maximum dose < 112%.

Trial Acronym/Author, Year, Study Design	Intervention(s) and Comparison	Dose and Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose)	Target Volumes	Planning Parameters
Rodrıguez, 2013,[25, 26] noninferiority RCT	APBI (3DCRT)	37.5 Gy in 10 fractions, twice daily	CTV: NR PTV: Entire quadrant as primary tumor site.	Ipsilateral breast: Recorded the volume receiving 50% of the prescription dose Ipsilateral lung: Recorded the volume receiving ≥ 10 Gy. Heart: Recorded the volume receiving ≥ 2 Gy and ≥ 15 Gy.
	WBI	48 Gy in 24 fractions, once daily Boost to the lumpectomy cavity: 10 Gy (received by 66%)	CTV: NR PTV: NR	PTV: Coverage with ≥ 95% isodose line while maintaining hot spot < 105%. Image guidance: Portal images on day 1 and 2, then weekly
Song, 2021[27]	PBI (3DCRT)	40 Gy in 10 fractions daily	CTV: Tumor bed + 1.5 cm. PTV: 0.6 cm (limited 0.5 cm under skin).	V43Gy < 5%, Dmax < 44; Breast –PTV: V20 Gy < 60%, V40 Gy < 35% Dmax < 44 Gy
	WBI	43.5 Gy in 15 fractions daily	CTV: Whole breast including fascia. PTV: 0.6 cm.	V47Gy< 5

Trial Acronym/Author, Year, Study Design	Intervention(s) and Comparison	Dose and Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose)	Target Volumes	Planning Parameters
TARGIT-A,[28-37] NCT00983684/ISRCTN34086741, noninferiority RCT	APBI (IORT)	20 Gy in one fraction Prescribed as 20 Gy to the surface of the applicator, or as 6 Gy at 1 cm	CTV and PTV: NR	NR.
	WBI	Once daily (Planning protocols for WBI were defined by each center and were not centrally defined)	CTV and PTV: NR.	NR.
Yadav, 2020,[38] noninferiority RCT	APBI (3DCRT)	34 Gy in 10 fractions, twice daily, over 5 days	CTV: 1 cm margin on cavity. PTV: 1 cm.	Ipsilateral breast: V50% < 50%, V100% < 25%. Ipsilateral lung: <10% of the lung should receive 30% of the prescribed dose. Heart: <5% of the heart should receive 5% of the prescribed dose. PTV: 95% of prescription dose delivered to at least 95% of PTV
	WBI	40 Gy in 16 fractions once daily, over 3 weeks + optional boost of 10-16 Gy in 5-8 fractions boost over 1-1.5 week (received by 56%).	CTV: Whole breast. PTV: NR.	Ipsilateral lung: <10% of the lung should receive 30% of the prescribed dose. Heart: <5% of the heart should receive 5% of the prescribed dose. PTV: 95% of prescription dose delivered to at least 95% of PTV Image guidance: portal images on fractions 1 and 2, then weekly

Abbreviations: 2DRT = 2-dimensional radiotherapy; 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; cm = centimeter; CT = computed tomography; CTV = clinical target volume; Gy = gray; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key

Question; mm = millimeter; NR = not reported; PBI = partial breast irradiation; PTV = planning target volume; RCT = randomized clinical trial; V = volume of a structure receiving a given dose of radiotherapy expressed as either a percentage of the prescription dose (e.g. V100%) or as a quantity of dose (e.g. V30Gy); WBI = whole breast irradiation

Table E.2. Characteristics of interventions. KQ 2: Comparisons of different PBI modalities

Trial Acronym, Author, Year, Study Design	Intervention(s) and Comparison	Dose-Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose, EQD2)	Target Volumes	Planing Parameters
Budapest,[2] 2007,[1, 3] 2013,[4] 2021,[5] noninferiority RCT	APBI (multi-catheter interstitial brachytherapy)	36.4 Gy in 7 fractions, twice daily	PTV: 2 cm.	Brachytherapy Goals NR, V100, V150, Dose-non uniformity ratio reported. Skin Max <60% Prescription.
	APBI (3DCRT)	50 Gy in 25 fractions, once daily	PTV: 2 cm.	Brachytherapy Goals NR, V100, V150, Dose-non uniformity ratio reported. Skin Max <60% Prescription.
	WBI	50 Gy in 25 fractions, once daily	PTV: Whole breast.	NR.
Bush, 2011,[39] 2014,[40] NCT00614172, single-arm observational study	APBI (proton radiation therapy)	40 Gy in 10 fractions, once daily	CTV: 1 cm.	Ipsilateral breast: Reported the mean volume of breast receiving 36 Gy was 12%. Approximately two-thirds of nontargeted breast tissue received doses <20 Gy. Skin: Goal was to minimize the volume of skin encompassed by 90% of the isodose line. Reported the mean volume of skin receiving 36 Gy was 5%. Reported minimal or no measurable dose delivered to the lung, heart, or contralateral breast. Image guidance (use of clips for localization): 100%.

Trial Acronym, Author, Year, Study Design	Intervention(s) and Comparison	Dose-Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose, EQD2)	Target Volumes	Planing Parameters
Galland-Girodet, 2014,[41] NCT00694577, comparative observational study	APBI (3DCRT)	32 Gy in 8 fractions, twice daily	PTV: Lumpectomy cavity expanded by 1.5-2 cm.	Ipsilateral breast: PTV volume was recommended to be less than 30%-35% of the breast volume. Nontarget breast tissue was preferred to receive <50% of prescribed dose, but this was not mandated. Ipsilateral lung: Volume receiving 10 Gy reported as 3.8%. Heart: Dose received by 5% of heart volume reported as 3.1%.
	APBI (passive scatter proton radiation therapy)	32 Gy in 8 fractions, twice daily	PTV: Lumpectomy cavity expanded by 1.5-2 cm.	Ipsilateral breast: PTV volume was recommended to be less than 30%-35% of the breast volume. Non-target breast tissue was preferred to receive <50% of prescribed dose, but this was not mandated. Ipsilateral lung: Volume receiving 10 Gy reported as 1.8%. Heart: Dose received by 5% of heart volume reported as 0.1%.

Trial Acronym, Author, Year, Study Design	Intervention(s) and Comparison	Dose-Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose, EQD2)	Target Volumes	Planing Parameters
Jacobs, 2018,[42] 2019,[43-45] comparative observational study	APBI (IORT)	23.3 Gy in one fraction at the 100% isodose line	CTV: 2 cm lateral margin on clips or cavity.	6-12 MeV using 4 – 6.5 cm cone, 23.3 Gy prescribed to the 100% isodose line, with the aim to cover the full thickness of glandular breast tissue with 21 Gy
	APBI (3DCRT or IMRT)	3.85 Gy in 10 fractions, once daily for a total of 38.5 Gy	CTV: Clips plus 1.5 cm. PTV: 0.7-0.9 cm, trimmed 0.5 cm under skin.	Ipsilateral Breast ≤ 35% received 100% of the prescribed dose. Mandatory for inclusion PTV goal: ≥ 98% of the PTV received ≥ 95% of the prescribed dose. At least 90% of the PTV was required to received ≥ 90% of the prescribed dose.
Leonard, 2021[46]	APBI (3DCRT)	38.5 Gy in 10 fractions, twice daily, for 5 days	CTV: Lumpectomy cavity with 1 cm margin. PTV: 0.5 cm margin, excluding 0.5 cm below skin.	Minimum of 4 fields
	APBI (IMRT)	38.5 Gy in 10 fractions, twice daily, for 5 days	CTV: Lumpectomy cavity with 1 cm margin. PTV: 0.5 cm margin, excluding 0.5 cm below skin.	Sliding window or step and shoot D95%>95% CTV D95% > 95% PTV

Trial Acronym, Author, Year, Study Design	Intervention(s) and Comparison	Dose-Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose, EQD2)	Target Volumes	Planing Parameters
Meszaros, 2020,[47] NCT02003560, comparative observational study	APBI (3DCRT)	36.9 Gy in 9 fractions, twice daily	CTV: 2 cm-minimum margin free in six directions. PTV: 0.5 cm.	All had clips for localization. IGRT used. Ipsilateral breast: V100 ≤ 35% and V50 ≤60%. Heart: V15≤10%.
	APBI (IMRT)	36.9 Gy in 9 fractions, twice daily	CTV: 2 cm-minimum margin free in six directions. PTV: 0.5 cm.	All had clips for localization. IGRT used. Ipsilateral breast: V100 ≤35% and V50 ≤60%. Heart: V15≤10%.
Mutter, 2019,[48] single-arm observational study	APBI (proton radiation therapy)	21.9 Gy in 3 fractions, daily	CTV: Postoperative tumor bed with a 1 cm expansion. PTV: 0.3 cm.	All had clips for localization. All underwent IGRT with kV. Ipsilateral breast V50% < 35% and V100% < 20%. Heart D0.01cc of the heart < than 1 Gy.
Pasalic, 2021,[49] NCT01245712, single-arm observational study	APBI (proton radiation therapy)	34 Gy in 10 fractions, twice daily	CTV: 1.5 cm. PTV: 0.5 cm.	All had clips for localization with IGRT. CTV V100 > 95%. PTV coverage : ≥ D90 > 90%, Max dose < 120%. Ipsilateral breast: V100 < 35% and V50 < 50%. Ipsilateral lung: V30 < 15%. Right-sided: heart V5 < 5%, Left-sided: heart V5 < 40%.

Trial Acronym, Author, Year, Study Design	Intervention(s) and Comparison	Dose-Fraction Schemes (Frequency, Total Number of Radiation Treatments, Total Prescribed Dose, EQD2)	Target Volumes	Planing Parameters
Shah, 2004,[50] comparative observational study	APBI (multi-catheter interstitial brachytherapy)	34 Gy in 10 fractions, twice daily	CTV: 2 cm.	NR.
	APBI (single-entry catheter brachytherapy)	34 Gy in 10 fractions, twice daily	CTV: volume of balloon + 1 cm.	NR. Distance ≥ 5 mm between balloon and skin.
Shah, 2012,[51] comparative observational study	APBI (multi-catheter interstitial brachytherapy)	50 Gy in one fraction over 96 hours, or 32 Gy in 8 fractions, and 34 in 10 fractions, twice daily	NR.	NR.
	APBI (single-entry catheter brachytherapy)	Twice daily (32 Gy in 8 fractions or 34 Gy in 10 fractions delivered twice daily)	NR.	NR.
	APBI (3DCRT)	38.5 Gy in 10 fractions, twice daily	CTV: 1.0 – 1.5 cm. PTV: 0.5-1.0 cm.	CTV: V100: 100%. PTV: D100 > 90%, Max dose < 110% Ipsilateral Breast.
Stecklein, 2019,[52] comparative observational study	APBI (single-entry catheter brachytherapy)	34 Gy in 10 fractions, twice daily	PTV: 1 cm.	Ipsilateral Breast V150 < 50 cc, V200 < 20 cc (SAVI) or < 10 cc for Contura and MammoSite.
	APBI (3DCRT)	38.5 Gy in 10 fractions (except for 2 patients, [34 Gy]), twice daily	CTV and PTV: 2.5 cm.	PTV: D95% ≥95% D90 > 90% was considered acceptable.

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy ; APBI = accelerated partial breast irradiation; cc = cubic centimeter; cm = centimeter; CTV = clinical target volume; EQD2 = equivalent dose in 2 Gy fractions; Gy = gray; IGRT = image-guided radiation therapy; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; kV = kilovoltage; MeV = megaelectron volt; mm = millimeter; NR = not reported; PBI = partial breast irradiation; PTV = planning target volume; RCT = randomized clinical trial; SAVI = Strut-Adjusted Volume Implant; V = volume of a structure receiving a given dose of radiotherapy expressed as either a percentage of the prescription dose (e.g. V100%) or as a quantity of dose (e.g. V30Gy); WBI = whole breast irradiation

Appendix F. Risk of Bias

Table F.1. Risk of bias (Cochrane ROB tool) for included randomized clinical trial studies

Trial Acronym/Author Year	Overall ROB	ROB From Randomization Process	ROB Due to Deviations From Intended Interventions	ROB Due to Missing Outcome Data	ROB in Measurement of Outcomes	ROB in Selection of the Reported Results
Budapest,[2] 2007,[1, 3] 2013,[4] 2021[5]	High	High	Low	Low	Low*	Low
Dodwell, 2005[6]	High	High	Moderate	High	Low	Low
ELIOT[7, 8]	Low	Low	Low	Low	Low	Low
Florence[9-13]	Low*	Low	Low	Low	Low*	Low
GEC-ESTRO[14-17]	Moderate*	Low	Moderate	Low	Low*	Low
HYPAB[18]	High	Moderate	Moderate	Low	Moderate*	High
Leonard, 2021[46]	High	Moderate	High	Low	Moderate	Low
NSABP B-39/RTOG 0413[19]	Low	Low	Low	Low	Low	Low
UK IMPORT LOW[20, 21]	Low	Low	Low	Low	Low	Low
RAPID[22-24]	Low*	Low	Low	Low	Low*	Low
Rodrıguez, 2013[25, 26]	High	Moderate	High	High	Low*	Low
Song, 2021[27]	High	Moderate	High	Low	Moderate	Low
TARGIT-A[28-37]	Low	Low	Low	Low	Low	Low
Yadav, 2020[38]	High	Moderate	High	High	Low*	Low

Abbreviations: ROB = risk of bias

*As cosmetic outcomes were also evaluated by non-blinded patients and/or providers and were likely to be biased, the studies were rated as high risk of bias in "measurement of outcomes" and "overall risk of bias" for cosmetic outcomes.

Table F.2. Risk of bias (Newcastle Ottawa tool) for included comparative studies

Trial Acronym/Author Year	Overall ROB	Representativeness of Study Cohort	Ascertainment of Exposure	Outcome Not Present Before the Exposure	Comparability Between Groups	Outcome Data Source	Independent Blind Assessment of Outcome	Loss During Followup	Length of Followup
Galland-Girodet, 2014[41]	High	High	Low	Low	High	Low	High	Low	Low
Jacobs, 2022,[45] and 2018[42-44]	High	High	Low	Low	High	Low	Low	Low	Low
Meszaros, 2020[47]	High	High	Low	Low	High	Low	High	Moderate	Low
Shah, 2004[50]	High	High	Low	Low	High	Low	High	Moderate	Low
Shah, 2012[51]	High	Low	Low	Low	High	Low	High	Moderate	High
Stecklein, 2019[52]	High	High	Low	Low	High	Low	High	Moderate	Low

Abbreviations: ROB = risk of bias

Table F.3. Risk of bias (Newcastle Ottawa tool) for included single-arm observational studies

Trial Acronym/Author Year	Overall ROB	Representativeness of Study Cohort	Ascertainment of Exposure	Outcome Not Present Before the Exposure	Outcome Data Source	Independent Blind Assessment of Outcome	Loss During Followup	Length of Followup
Bush, 2011,[39] 2014[40]	High	Moderate	Low	Low	Low	High	Moderate	Low
Mutter, 2019[48]	High	Moderate	Low	Low	Moderate	High	Low	High
Pasalic, 2021[49]	High	Low	Low	Low	Low	High	Low	High

Abbreviations: ROB = risk of bias

Appendix G. Results From Included Studies

Table G.1. KQ 1. Results by study

Trial Acronym/Author Year, Trial Registration, Study Design	Intervention(s) and Comparator	Dose-Fractionation Schemes	Conclusion (Effectiveness and Toxicity)
Budapest,[2] 2007,[1, 3] 2013,[4] 2021,[5] noninferiority RCT	APBI (multi-catheter interstitial brachytherapy, or 3DCRT) vs. WBI	36.4 Gy in 7 fractions, twice daily (multi-catheter interstitial brachytherapy), or 50 Gy in 25 fractions, once daily (3DCRT) vs. 50 Gy in 25 fractions, once daily	There was no statistical difference between APBI and WBI on IBR, overall survival, or disease-free survival at 5 years, 10 years, and 20 years. There was no significant difference on cosmesis at 5 years. However, significantly fewer patients reported poor or fair cosmetic results in the APBI group than those in the WBI group at 10 years and 20 years. There was no statistical difference between APBI (multi-catheter interstitial brachytherapy, or limited field electron beam radiotherapy) and APBI (3DCRT) on cosmesis at 5 years, 10 years, and 20 years.
Dodwell, 2005,[6] RCT	Nonaccelerated PBI (3DCRT/2DRT, and electrons) vs. WBI	55 Gy in 20 fractions, once daily, over 4 weeks vs. 40 Gy in 15 fractions, once daily, over 3 weeks + 15 Gy in 5 fractions boost	At a median followup of 8 years, there was no significant difference on IBR, overall survival, or distant recurrence between PBI and WBI.
ELIOT,[7, 8] NCT01849133, equivalence RCT	APBI (IORT) vs. WBI	21 Gy in one fraction, once vs. 50 Gy in 25 fractions	The IORT group reported significantly higher IBR than the WBI group at 5 years, 10 years, and 15 years, however, the difference was within the prespecified equivalence margin at 5 years. There was no significant difference on overall survival at 5 years. The IORT group was associated with significantly fewer skin adverse events.
Florence,[9-13] NCT02104895, equivalence RCT	APBI (IMRT) vs. WBI	30 Gy in 5 fractions, once every 2 days vs. 50 Gy in 25 fractions, once daily	There was no significant difference on IBR or overall survival at 5 years and 10 years between the two groups. The IMRT group reported significantly better outcomes on acute and late toxicity and cosmetic outcomes at 5 years and 10 years. The IMRT group was also associated with significantly better quality of life (global health status, functional and symptom) measured by EORTC QLQ-C30 scales and symptom scales (breast and arm symptoms) measured by EORTC QLQ-BR23 at 2 years.

Trial Acronym/Author Year, Trial Registration, Study Design	Intervention(s) and Comparator	Dose-Fractionation Schemes	Conclusion (Effectiveness and Toxicity)
GEC-ESTRO,[14-17] NCT00402519, noninferiority RCT	APBI (multi-catheter interstitial brachytherapy) vs. WBI	HDR brachytherapy: 32 Gy in 8 fractions or 30.3 Gy in 7 fractions, twice daily. PDR-brachytherapy: 0.60-0.80 Gy/hour to 50 Gy (1 pulse/hour, 24 hours/day) vs. 50 Gy (50-50.4 Gy) in 25-28 fractions, once daily (Monday-Friday), for 6-7 weeks + 10 Gy boost	Multi-catheter interstitial brachytherapy was not inferior to WBI on IBR, cancer-free survival, and overall survival at 5 years. The multi-catheter interstitial brachytherapy group reported significantly less acute skin toxicity. There was no significant difference on late adverse events, patient and physician rated cosmetic outcomes at 5 years. Multi-catheter interstitial brachytherapy was associated with better breast symptoms and arm symptoms after radiation therapy, 3-month followup, and 5-year followup (measured by EORTC QLQ-BR23). There was no significant difference in global health status at 5 years (measured by EORTC QLQ-C30).
HYPAB,[18] RCT	APBI (IMRT) vs. WBI	30 Gy in 5 fractions, on alternate days vs. 40.5 in 15 fractions, once daily, over 3 weeks + 48 Gy integrated boost	At a median followup of 3 years, there was no significant difference on IBR, overall survival, and physician-rated cosmesis. IMRT was associated with significantly fewer acute and late adverse events.
NSABP B-39/RTOG 0413,[19] NCT00103181, equivalence RCT	APBI (single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, 3DCRT) vs. WBI	Brachytherapy: 34 Gy in 10 fractions, twice daily 3DCRT: 38.5 Gy in 10 fractions, twice daily vs. 50 Gy in 25 fractions, 5 days/week	The APBI group did not meet the criteria for equivalence to WBI in preventing IBR at 10 years. There was no significant difference on overall survival, cancer free survival, and adverse events.
UK IMPORT LOW,[20, 21] ISRCTN12852634, noninferiority RCT	Nonaccelerated PBI (3DCRT) vs. WBI	40 Gy in 15 fractions, once daily vs. 40 Gy in 15 fractions, once daily	Nonaccelerated 3DCRT was noninferior to WBI on IBR at 5 years. There was no significant difference on overall survival at 5 years. Significantly lower adverse events per patient was reported by the 3DCRT group.
RAPID,[22-24] NCT00282035, noninferiority RCT	APBI (3DCRT) vs. WBI	38.5 Gy in 10 fractions, twice daily vs. 42.5 Gy in 16 fractions or 50 Gy in 25 fractions, once daily	APBI was noninferior to WBI in preventing IBR at 5 years. There was no significant difference on IBR and overall survival at 8 years. Significantly fewer acute adverse events and more late adverse events and poor or fair cosmetic outcomes (patients and nurse rated) were reported by the APBI group.
Rodrıguez, 2013,[25, 26] noninferiority RCT	APBI (3DCRT) vs. WBI	37.5 Gy in 10 fractions, twice daily vs. 48 Gy in 24 fractions, once daily	At a median followup of 5 years, there was no statistical difference on overall survival, cosmesis, and late toxicity between the two groups. Significantly fewer patients in the 3DCRT group reported grade 2 or above acute skin toxicity than those in the WBI group. No patients reported local, regional, or distant recurrence.

Trial Acronym/Author Year, Trial Registration, Study Design	Intervention(s) and Comparator	Dose-Fractionation Schemes	Conclusion (Effectiveness and Toxicity)
TARGIT-A,[28-37] NCT00983684/ISRCTN34086741, noninferiority RCT	APBI (IORT) vs. WBI	20 Gy in one fraction, once vs. once daily (Planning protocols for WBI were defined by each center and were not centrally defined) vs 40.5-42.6 Gy in 16 fractions or 50.0-50.4 Gy in 25-26 fractions + 10-14 Gy boost	IORT was noninferior to WBI in preventing IBR at 5 years. IORT was associated with significantly more overall survival at 5 years. There was no significant difference on overall survival or mastectomy-free survival at 12 years. Significantly fewer grade 3 or 4 skin adverse events (<6 months after randomization) were reported with IORT. The total number of adverse events were similar between the two groups. In a sub-study of the TARGIT-A trial (West Australia, n=385), there was no significant difference on cosmesis at 5 years; while significantly and clinically significant better breast-related breast symptoms and arm concerns (measured by EORTC QLQ BR23) was reported in the IORT group at 5 years.
Yadav, 2020,[38] noninferiority RCT	APBI (3DCRT) vs. WBI	34 Gy in 10 fractions, twice daily, over 5 days vs. 40 Gy in 16 fractions once daily, over 3 weeks + 10-16 Gy in 5-8 fractions boost over 1-1.5 week	At a median followup of 5 years, significantly fewer patients in the 3DCRT group reported poor/fair cosmetic outcomes and late adverse events than those in the WBI group.
Song, 2021,[27] NCT03583619, RCT	APBI (3DCRT) vs. WBI	40 Gy in 10 fractions daily vs. 43.5 Gy in 15 fractions daily	At a median followup of 2.16 years, no patients died or reported relapse. There was no significant difference between the two groups in any subscales measured by EORTC QLQ -C30 and EORTC QLQ-BR23 at 1 year.

Abbreviations: 2DRT = 2-dimensional radiotherapy; 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; EORTC QLQ-BR23 = European Organization for Research and Treatment of Cancer quality of life questionnaire-BR 23; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire-C30; Gy = gray; HDR = high dose rate; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiotherapy; IORT = intraoperative radiotherapy; KQ = Key Question; PBI = partial breast irradiation; PDR = pulsed dose rate; RCT = randomized clinical trial; WBI = whole breast irradiation

Table G.2. KQ 2. Results by study

Trial Acronym/Author Year, Trial Registration, Study Design	Intervention(s) and Comparator	Dose-Fractionation Schemes	Conclusion (Effectiveness and Toxicity)
Bush, 2011,[39] 2014,[40] NCT00614172, single-arm observational study	APBI (proton radiation therapy)	40 Gy in 10 fractions, once daily	At a median followup of 5 years, the overall survival and disease-free survival was 95% and 94%, respectively. No acute adverse events of grade 3 or higher was reported. Grade 1 or 2 acute radiation dermatitis was reported in 62% of the patients. Late skin toxicity included 7 cases of grade 1 telangiectasis. Over 90% of the patients and physicians reported good or excellent cosmesis.
Galland-Girodet, 2014,[41] NCT00694577, comparative observational study	APBI (3DCRT) vs. APBI (proton radiation therapy)	32 Gy in 8 fractions, twice daily vs. 32 Gy in 8 fractions, twice daily	At a median followup of 6.8 years, significantly fewer patients in the 3DCRT group reported fair or poor cosmesis (assessed by physicians) and less late toxicity than those in the proton radiation therapy group. There was no significant difference on patient reported cosmetic outcomes and IBR.
Jacobs, 2018,[42] 2019,[43] 2021,[44] 2022,[45] comparative observational study	APBI (IORT) vs. APBI (3DCRT or IMRT)	23.3 Gy in one fraction at the 100% isodose line vs. 3.85 Gy in 10 fractions, once daily for a total of 38.5 Gy	At a followup of 5 years, the IORT group reported significantly more IBR than the 3DCRT or IMRT group. Significantly more patients in the IORT group reported grade 2 or higher acute adverse events at 3 months. There was no significant difference on grade 3 adverse events. No grade 4 adverse events were reported in either group. At 1 year, there was no clinically relevant difference in quality of life measured by EORTC QLQ-C30 (version 3) and EORTC QLQ BR23.
Leonard, 2021,[46] NCT01185132/NCT01185145, RCT	APBI (3DCRT) vs. APBI (IMRT)	38.5 Gy in 10 fractions BID (5 days) vs. 38.5 Gy in 10 fractions BID (5 days)	At 5 years, patients in the 3DCRT group reported significantly more cancer-free survival and better physician-assessed cosmesis than those in the IMRT group. There was no significantly difference in IBR, overall survival, and patients reported cosmesis.
Meszaros, 2020,[47] NCT02003560, comparative observational study	APBI (3DCRT) vs. APBI (IMRT)	36.9 Gy in 9 fractions, twice daily vs. 36.9 Gy in 9 fractions, twice daily	At a median followup of 7.5 years, there was no significant difference between the two group on IBR. Significantly more poor or fair cosmetic results (assessed by patients and physicians) were reported in the 3DCRT group than in the IMRT group. The 3DCRT group also reported significantly more acute and late adverse events than the IMRT group.
Mutter, 2019,[48] single-arm observational study	APBI (proton radiation therapy)	21.9 Gy in 3 fractions, daily	At a median followup of 1 year, no patient reported treatment-related adverse events of grade 2 or higher. The most common adverse events were dermatitis and skin hyperpigmentation. 98% of the patients reported good or excellent cosmesis and 93% of the patients reported quality of life as ≥7 out of 10 (10 indicating the best score).
Pasalic, 2021,[49] NCT01245712, single-arm observational study	APBI (proton radiation therapy)	34 Gy in 10 fractions, twice daily	At a median followup of 2 years, no patients reported IBR or died. There were no acute or late adverse events of grade 3 or higher. No patients reported fat necrosis, fibrosis, infection, or breast shrinkage. 93% of the patients and 83% of physicians reported excellent or good cosmetic results at 3 years.
Polgar, 2002,[2] 2007,[1, 3] 2013,[4] 2021,[5] noninferiority RCT	APBI (multi-catheter interstitial brachytherapy) vs. APBI (3DCRT)	36.4 Gy in 7 fractions, twice daily vs. 50 Gy in 25 fractions, once daily	There was no statistical difference between APBI (multi-catheter interstitial brachytherapy, or limited field electron beam radiotherapy) and APBI (3DCRT) on cosmesis at 5 years, 10 years, and 20 years.

Trial Acronym/Author Year, Trial Registration, Study Design	Intervention(s) and Comparator	Dose-Fractionation Schemes	Conclusion (Effectiveness and Toxicity)
Shah, 2004,[50] comparative observational study	APBI (multi-catheter interstitial brachytherapy) vs. APBI (single-entry catheter brachytherapy)	34 Gy in 10 fractions, twice daily vs. 34 Gy in 10 fractions, twice daily	Single-entry catheter brachytherapy was associated with significantly less grade 1 skin erythema and grade >1 subcutaneous fibrosis at 1 year than multi-catheter interstitial brachytherapy; however, the incidence of overall late adverse events was significantly different.
Shah, 2012,[51] comparative observational study	APBI (multi-catheter interstitial brachytherapy) vs. APBI (single-entry catheter brachytherapy) vs. APBI (3DCRT)	50 Gy in one fraction over 96 hours, or 32 Gy in 8 fractions, and 34 in 10 fractions, twice daily vs. Twice daily (Not clearly described. Presumably the dose was similar to the dose used for an HDR interstitial implant: 32 Gy in 8 fractions or 34 Gy in 10 fractions delivered twice daily) vs. 38.5 Gy in 10 fractions, twice daily	There was no significant difference between the three groups on IBR, overall survival at 5 years.
Stecklein, 2019,[52] comparative observational	APBI (single-entry catheter brachytherapy) vs. APBI (3DCRT)	34 Gy in 10 fractions, twice daily vs. 38.5 Gy in 10 fractions (except for 2 patients, [34 Gy]), twice daily	There was no significant difference on IBR and cosmesis at 5 years. 3DCRT reported significantly more acute adverse events than single-entry catheter brachytherapy.

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; BID = two times a day; EORTC QLQ-BR23 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-BR 23; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; Gy = gray; HDR = high dose rate; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiotherapy; IORT = intraoperative radiotherapy; KQ = Key Question; RCT = randomized clinical trial

Appendix H. Studies With Multimodalities in the PBI Arms

Table H.1. Studies in which the PBI arms included mixed modalities within the same study

Comparison	Outcome	Time	Findings	Study Design and Sample Size
Multi-modalities compared with WBI	Total AE	Late	IRR: 1.01; 95% CI: 0.68 to 1.50; I^2 = 0%	2 RCTs,[1-5, 19] 4,474 patients
	AE grade ≥ 2	Late	IRR: 0.84; 95% CI: 0.78 to 0.91; I^2 = N/A	1 RCT,[19] 4,216 patients
	Cancer-free survival	5 years	RR: 1.02; 95% CI: 0.94 to 1.10; I^2 = N/A	1 RCT,[1-5] 258 patients
	Cancer-free survival	10 years	RR: 0.97; 95% CI: 0.80 to 1.16; I^2 = 0%	2 RCTs,[1-5, 19] 4,474 patients
	Cancer-free survival	>10 years	RR: 1.02; 95% CI: 0.90 to 1.15; I^2 = N/A	1 RCT,[1-5] 258 patients
	Contralateral breast cancer recurrence	5 years	RR: 2.71; 95% CI: 0.73 to 9.98; I^2 = N/A	1 RCT,[1-5] 258 patients
	Contralateral breast cancer recurrence	10 years	RR: 1.16; 95% CI: 0.43 to 3.11; I^2 = N/A	1 RCT,[1-5] 258 patients
	Contralateral breast cancer recurrence	> 10 years	RR: 0.53; 95% CI: 0.26 to 1.10; I^2 = N/A	1 RCT,[1-5] 258 patients
	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 0.66; 95% CI: 0.44 to 1.00; I^2 = N/A	1 RCT,[1-5] 258 patients
	Cosmesis reported by healthcare provider (poor or fair)	10 years	RR: 0.57; 95% CI: 0.37 to 0.88; I^2 = N/A	1 RCT,[1-5] 258 patients
	Cosmesis reported by healthcare provider (poor or fair)	> 10 years	RR: 0.56; 95% CI: 0.37 to 0.85; I^2 = N/A	1 RCT,[1-5] 258 patients
	Distant breast cancer recurrence	5 years	RR: 1.02; 95% CI: 0.39 to 2.62; I^2 = N/A	1 RCT,[1-5] 258 patients
	Distant breast cancer recurrence	10 years	RR: 0.70; 95% CI: 0.31 to 1.59; I^2 = N/A	1 RCT,[1-5] 258 patients
	Distant breast cancer recurrence	> 10 years	RR: 0.80; 95% CI: 0.43 to 1.51; I^2 = N/A	1 RCT,[1-5] 258 patients
	Elsewhere IBR	5 years	RR: 1.52; 95% CI: 0.26 to 8.97; I^2 = N/A	1 RCT,[1-5]258 patients
	Elsewhere IBR	10 years	RR: 2.03; 95% CI: 0.38 to 10.90; I^2 = N/A	1 RCT,[1-5] 258 patients
	Elsewhere IBR	> 10 years	RR: 1.63; 95% CI: 0.55 to 4.83; I^2 = N/A	1 RCT,[1-5] 258 patients

Comparison	Outcome	Time	Findings	Study Design and Sample Size
Multi-modalities compared with WBI (continued)	IBR	5 years	RR: 1.52; 95% CI: 0.44 to 5.27; I^2 =N/A	1 RCT,[1-5] 258 patients
	IBR	10 years	RR: 1.26; 95% CI: 0.19 to 8.45; I^2 = 0%	2 RCTs,[1-5, 19] 4,474 patients
	IBR	> 10 years	RR: 1.22; 95% CI: 0.55 to 2.72; I^2 = N/A	1 RCT,[1-5] 258 patients
	Overall survival	5 years	RR: 1.02; 95% CI: 0.96 to 1.09; I^2 = N/A	1 RCT,[1-5] 258 patients
	Overall survival	10 years	RR: 1.02; 95% CI: 0.89 to 1.17; I^2 = 0%	2 RCTs,[1-5, 19] 4,474 patients
	Overall survival	> 10 years	RR: 0.99; 95% CI: 0.81 to 1.21; I^2 = N/A	1 RCT,[1-5] 258 patients
	Overall survival	> 10 years	HR: 0.98; 95% CI: 0.66 to 1.46; I^2 = N/A	1 RCT,[1-5] 258 patients
	Tumor bed IBR	5 years	RR: 1.02; 95% CI: 0.15 to 7.10; I^2 = N/A	1 RCT,[1-5] 258 patients
	Tumor bed IBR	10 years	RR: 0.76; 95% CI: 0.17 to 3.34; I^2 =N/A	1 RCT,[1-5] 258 patients
	Tumor bed IBR	> 10 years	RR: 0.85; 95% CI: 0.26 to 2.70; I^2 = N/A	1 RCT,[1-5] 258 patients
Multi-modalities compared to IORT	IBR	5 years	RR: 0.28; 95% CI: 0.13 to 0.60; I^2 = N/A	1 observational study,[42-45] 617 patients
	Overall survival	5 years	RR: 1.10; 95% CI: 0.96 to 1.04; I^2 = N/A	1 observational study,[42-45] 617 patients
	Cancer free survival	5 years	RR: 1.00; 95% CI: 0.99 to 1.02; I^2 = N/A	1 observational study,[42-45] 617 patients
	Tumor bed IBR	5 years	RR: 0.04; 95% CI: 0.00 to 0.71; I^2 = N/A	1 observational study,[42-45] 617 patients
	Elsewhere IBR	5 years	RR: 0.35; 95% CI: 0.14 to 0.87; I^2 = N/A	1 observational study,[42-45] 617 patients
	Distant breast cancer recurrence	5 years	RR: 0.30; 95% CI: 0.06 to 1.43; I^2 = N/A	1 observational study,[42-45] 617 patients
	Total AE	Acute	IRR: 0.64; 95% CI: 0.50 to 0.82; I^2 = N/A	1 observational study,[42-45] 617 patients
	AE grade ≥ 2	Acute	IRR: 0.38; 95% CI: 0.18 to 0.77; I^2 = N/A	1 observational study,[42-45] 617 patients

Abbreviations: AE = adverse event; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; IORT = intraoperative radiotherapy; IRR = incidence rate ratio; N/A = not applicable; PBI = partial breast irradiation; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Appendix I. Specific Adverse Events and Adverse Events by Grade

Table I.1. KQ 1. Specific adverse events

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
PBI compared with WBI	Breast edema	Acute	IRR: 0.70; 95% CI: 0.51 to 0.96; I^2 = N/A	PBI: 5.98% (64/1070) vs. WBI: 8.54% (91/1065)	1 RCT,[22-24] 2135 patients.
	Breast edema	Late	IRR: 0.53; 95% CI: 0.03 to 8.14; I^2 = 0%	PBI: 4.50% (33/734) vs. WBI: 8.50% (63/741)	2 RCTs,[20, 21, 38] 1475 patients.
	Cardiac	Late	IRR: 0.81; 95% CI: 0.22 to 3.00; I^2 = N/A	PBI: 0.60% (4/669) vs. WBI: 0.74% (5/674)	1 RCT,[20, 21] 1343 patients.
	Extremity	Late	IRR: 0.96; 95% CI: 0.17 to 5.29; I^2 = 0%	PBI: 8.16% (108/1324) vs. WBI: 8.46% (114/1347)	2 RCTs,[14-17, 20, 21] 2671 patients.
	General	Acute	IRR: 0.92; 95% CI: 0.73 to 1.15; I^2 = N/A	PBI: 12.99% (139/1070) vs. WBI: 14.18% (151/1065)	1 RCT,[22-24] 2135 patients.
	General	Late	IRR: 0.71; 95% CI: 0.54 to 0.92; I^2 = N/A	PBI: 14.05% (94/669) vs. WBI: 19.88% (134/674)	1 RCT,[20, 21] 1343 patients.
	Breast induration or fibrosis	Late	IRR: 1.15; 95% CI: 0.37 to 3.55; I^2 = 95.34%	PBI: 17,74% (398/2243) vs. WBI: 11.13% (250/2247)	6 RCTs,[1, 9-13, 20-25, 38] 4490 patients.
	Pain	Acute	IRR: 0.97; 95% CI: 0.3 to 3.12; I^2 = 0%	PBI: 13.45% (232/1725) vs. WBI: 13.98% (243/1738)	2 RCTs,[14-17, 22-24] 3463 patients.
	Pain	Late	IRR: 1.37; 95% CI: 0.62 to 3.00; I^2 = 77.43%	PBI: 11.29% (276/2445) vs. WBI: 9.54% (235.01/2463)	4 RCTs,[14-17, 20-25] 4908 patients.
	Pulmonary	Acute	IRR: 0.25; 95% CI: 0.05 to 1.17; I^2 = N/A	PBI: 0.19% (2/1070) vs. WBI: 0.75% (8/1065)	1 RCT,[22-24] 2135 patients.
	Pulmonary	Late	IRR: 1.01; 95% CI: 0.25 to 4.03; I^2 = N/A	PBI: 0.60% (4/669) vs. WBI: 0.59% (4/674)	1 RCT,[20, 21] 1343 patients.
	Rib fracture	Late	IRR: 0.34; 95% CI: 0.03 to 3.23; I^2 = N/A	PBI: 0.15% (1/669) vs. WBI: 0.45% (3/674)	1 RCT,[20, 21] 1343 patients.
	Skin	Acute	IRR: 0.28; 95% CI: 0.21 to 0.38; I^2 = 0%	PBI: 14.38% (285/1985) vs. WBI: 50.75% (1014/1998)	3 RCTs,[9-17, 22-24] 3983 patients.
	Skin	Late	IRR: 0.85; 95% CI: 0.54 to 1.34; I^2 = 31.83%	PBI: 8.86% (139/1568) vs. WBI: 10.09% (161/1595)	5 RCTs,[1, 14-17, 20, 21, 25, 38] 3163 patients.
	Soft tissue	Acute	IRR: 7.96; 95% CI: 2.81 to 22.56; I^2 = N/A	PBI: 4.73% (31/655) vs. WBI: 0.59% (4/673)	1 RCT,[14-17] 1328 patients.

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
PBI compared with WBI (continued)	Soft tissue	Late	IRR: 1.29; 95% CI: 0.36 to 4.66; I^2 = 90.6%	PBI: 14.53% (376/2587) vs. WBI: 11.35% (296/2609)	5 RCTs,[1, 14-17, 20-24, 38] 5196 patients.
	Wound	Acute	IRR: 7.78; 95% CI: 4.94 to 12.26; I^2 = N/A	PBI: 24.27% (159/655) vs. WBI: 3.12% (21/673)	1 RCT,[14-17] 1328 patients.
	Telangiectasia	Late	IRR: 1.40; 95% CI: 0.00 to ∞; I^2 = 81.31%	PBI: 5.98% (104/1739) vs. WBI: 2.70% (47/1739)	2 RCTs,[20-24] 3478 patients.
3DCRT compared with WBI	Breast edema	Acute	IRR: 0.70; 95% CI: 0.51 to 0.96; I^2 = N/A	3DCRT: 5.98% (64/1070) vs. WBI: 8.54% (91/1065)	1 RCT,[22-24] 2135 patients.
	Breast edema	Late	IRR: 0.53; 95% CI: 0.03 to 8.14; I^2 = 0%	3DCRT: 4.50% (33/734) vs. WBI: 8.50% (63/741)	2 RCTs,[20, 21, 38] 1475 patients.
	Breast induration or fibrosis	Late	IRR: 1.49; 95% CI: 0.20 to 10.84; I^2 = 96.68%	3DCRT: 18.01% (334/1855) vs. WBI: 9.37% (174/1857)	4 RCTs,[20-25, 38] 3712 patients.
	Cardiac	Late	IRR: 0.81; 95% CI: 0.22 to 3.00; I^2 = N/A	3DCRT: 0.60% (4/669) vs. WBI: 0.74 % (5/674)	1 RCT,[20, 21] 1343 patients.
	Extremity	Late	IRR: 1.00; 95% CI: 0.75 to 1.32; I^2 = N/A	3DCRT: 14.50% (97/669) vs. WBI: 14.54% (98/674)	1 RCT,[20, 21] 1343 patients.
	General	Acute	IRR: 0.92; 95% CI: 0.73 to 1.15; I^2 = N/A	3DCRT: 12.99% (139/1070) vs. WBI: 14.18% (151/1065)	1 RCT,[22-24] 2135 patients.
	General	Late	IRR: 0.71; 95% CI: 0.54 to 0.92; I^2 = N/A	3DCRT: 14.05% (94/669) vs. WBI: 19.88% (134/674)	1 RCT,[20, 21] 1343 patients.
	Pain	Acute	IRR: 0.86; 95% CI: 0.63 to 1.18; I^2 = N/A	3DCRT: 6.64% (71/1070) vs. WBI: 7.70% (82/1065)	1 RCT,[22-24] 2135 patients.
	Pain	Late	IRR: 1.49; 95% CI: 0.18 to 12.69; I^2 = 84.14%	3DCRT: 9.55% (171/1790) vs. WBI: 8.44% (151.01/1790)	3 RCTs,[20-26] 3580 patients.
	Pulmonary	Acute	IRR: 0.25; 95% CI: 0.05 to 1.17; I^2 = N/A	3DCRT: 0.19% (2/1070) vs. WBI: 0.75% (8/1065)	1 RCT,[22-24] 2135 patients.
	Pulmonary	Late	IRR: 1.01; 95% CI: 0.25 to 4.03; I^2 = N/A	3DCRT: 0.60% (4/669) vs. WBI: 0.59% (4/674)	1 RCT,[20, 21] 1343 patients.
	Rib fracture	Late	IRR: 0.34; 95% CI: 0.03 to 3.23; I^2 = N/A	3DCRT: 0.15% (1/669) vs. WBI: 0.45% (3/674)	1 RCT,[20, 21] 1343 patients.
	Skin	Acute	IRR: 0.31; 95% CI: 0.25 to 0.39; I^2 = N/A	3DCRT: 9.53% (102/1070) vs. WBI: 30.80% (328/1065)	1 RCT,[22-24] 2135 patients.
	Skin	Late	IRR: 0.63; 95% CI: 0.29 to 1.40; I^2 = 0%	3DCRT: 6.11% (48/785) vs. WBI: 9.72% (77/792)	3 RCTs,[20, 21, 25, 38] 1577 patients.

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
3DCRT compared with WBI (continued)	Soft tissue	Late	IRR: 1.39; 95% CI: 0.03 to 63.53; I^2 = 94.48%	3DCRT: 7.37% (133/1804) vs. WBI: 6.42% (116/1806)	3 RCTs,[20-24, 38] 3610 patients.
	Telangiectasia	Late	IRR: 1.40; 95% CI: 0.00 to ∞; I^2 = 81.31%	3DCRT: 5.98% (104/1739) vs. WBI: 2.70% (47/1739)	2 RCTs,[20-24] 3478 patients.
IMRT compared with WBI	Breast induration or fibrosis	Late	IRR: 0.43; 95% CI: 0.22 to 0.84; I^2 = N/A	IMRT: 4.62% (12/260) vs. WBI: 10.77% (28/260)	1 RCT,[9-13] 520 patients.
	Skin	Acute	IRR: 0.28; 95% CI: 0.21 to 0.39; I^2 = N/A	IMRT: 18.85% (49/260) vs. WBI: 66.54% (173/260)	1 RCT,[9-13] 520 patients.
IORT compared with WBI	Skin	Acute	IRR: 0.50; 95% CI: 0.00 to +∞; I^2 = 93.83%	IORT: 1.52% (36/2372) vs. WBI: 2.22% (53/2384)	2 RCTs,[7, 8, 28-37] 4756 patients.
	Skin	Late	IRR: 0.91; 95% CI: 0.00 to 339.55; I^2 = 0%	IORT: 0.38% (9/2372) vs. WBI: 0.42% (10/2384)	2 RCT,[7, 8, 28-37] 4756 patients.
	Wound	Acute	IRR: 1.81; 95% CI: 1.16 to 2.83; I^2 = N/A	IORT: 3.14% (54/1721) vs. WBI: 1.73% (30/1730)	1 RCT,[28-37] 3451 patients.
	Wound	Late	IRR: 1.46; 95% CI: 0.68 to 3.15; I^2 = N/A	IORT: 0.93% (16.01/1721) vs. WBI: 0.64% (11.01/1730)	1 RCT,[28-37] 3451 patients.

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
Multi-catheter interstitial brachytherapy compared with WBI	Extremity	Late	IRR: 0.71; 95% CI: 0.33 to 1.52; I^2 = N/A	Multi-catheter interstitial brachytherapy: 1.68% (11/655) vs. WBI: 2.38% (16/673)	1 RCT,[14-17] 1328 patients.
	Pain	Acute	IRR: 1.03; 95% CI: 0.83 to 1.28; I^2 = N/A	Multi-catheter interstitial brachytherapy: 24.58% (161/655) vs. WBI: 23.92% (161/673)	1 RCT,[14-17] 1328 patients.
	Pain	Late	IRR: 1.28; 95% CI: 0.96 to 1.71; I^2 = N/A	Multi-catheter interstitial brachytherapy: 16.03% (105/655) vs. WBI: 12.48% (84/673)	1 RCT,[14-17] 1328 patients.
	Skin	Acute	IRR: 0.27; 95% CI: 0.22 to 0.32; I^2 = N/A	Multi-catheter interstitial brachytherapy: 20.46% (134/655) vs. WBI: 76.23% (513/673)	1 RCT,[14-17] 1328 patients.
	Skin	Late	IRR: 1.03; 95% CI: 0.74 to 1.43; I^2 = N/A	Multi-catheter interstitial brachytherapy: 10.53% (69/655) vs. WBI: 10.25% (69/673)	1 RCT,[14-17] 1328 patients.
	Soft tissue	Acute	IRR: 7.96; 95% CI: 2.81 to 22.56; I^2 = N/A	Multi-catheter interstitial brachytherapy: 4.73% (31/655) vs. WBI: 0.59% (4/673)	1 RCT,[14-17] 1328 patients.
	Soft tissue	Late	IRR: 1.47; 95% CI: 1.18 to 1.82; I^2 = N/A	Multi-catheter interstitial brachytherapy: 31.15% (204/655) vs. WBI: 21.25% (143/673)	1 RCT,[14-17] 1328 patients.
	Wound	Acute	IRR: 7.78; 95% CI: 4.94 to 12.26; I^2 = N/A	Multi-catheter interstitial brachytherapy: 24.27% (159/655) vs. WBI: 3.12% (21/673)	1 RCT,[14-17] 1328 patients.
Multi-modalities compared with WBI	Breast induration or fibrosis	Late	IRR: 1.10; 95% CI: 0.74 to 1.63; I^2 = N/A	Multi-modalities: 40.63% (52/128) vs. WBI: 36.92% (48/130)	1 RCT,[1-5] 258 patients.
	Skin	Late	IRR: 1.19; 95% CI: 0.68 to 2.08; I^2 = N/A	Multi-modalities: 21.09% (27/128) vs. WBI: 17.69% (23/130)	1 RCT,[1] 258 patients

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
	Soft tissue	Late	IRR: 1.07; 95% CI: 0.68 to 1.68; I^2 = N/A	Multi-modalities: 30.47% (39/128) vs. WBI: 28.46% (37/130)	1 RCT,[1] 258 patients

Abbreviations: ∞ = infinity; 3DCRT = 3-dimensional conformal external beam radiation therapy; CI = confidence interval; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; IRR = incidence rate ratio; KQ = Key Question; N/A = not applicable; PBI = partial breast irradiation; RCT = randomized clinical trial; WBI = whole breast irradiation

Table I.2. KQ 2. Specific adverse events

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
IMRT compared with 3DCRT	Breast induration or fibrosis	Late	IRR: 0.18; 95% CI: 0.07 to 0.45; I^2 = N/A	IMRT: 10% (6/60) vs. 3DCRT: 54.55% (24/44)	1 Observational study,[47] 104 patients.
	Pain	Acute	IRR: 0.29; 95% CI: 0.13 to 0.67; I^2 = N/A	IMRT: 13.33% (8/60) vs. 3DCRT: 45.45% (20/44)	1 Observational study,[47] 104 patients.
	Pain	Late	IRR: 4.40; 95% CI: 0.53 to 36.55; I^2 = N/A	IMRT: 10% (6/60) vs. 3DCRT: 2.27% (1/44)	1 Observational study,[47] 104 patients.
	Rib fracture	Late	IRR: 2; 95% CI: 0.18 to 22.06; I^2 = N/A	IMRT: 0.61% (2/328) vs. 3DCRT: 0.30% (1/328)	1 RCT,[46] 656 patients.
	Skin	Acute	IRR: 0.51; 95% CI: 0.30 to 0.87; I^2 = N/A	IMRT: 38.33% (23/60) vs. 3DCRT: 75% (33/44)	1 Observational study,[47] 104 patients.
	Skin	Late	IRR: 0.84; 95% CI: 0.30 to 2.31; I^2 = N/A	IMRT: 13.33% (8/60) vs. 3DCRT: 15.91% (7/44)	1 Observational study,[47] 104 patients.
	Soft tissue	Acute	IRR: 0.84; 95% CI: 0.46 to 1.54; I^2 = N/A	IMRT: 38.33% (23/60) vs. 3DCRT: 45.45% (20/44)	1 Observational study,[47] 104 patients.
	Soft tissue	Late	IRR: 0.49; 95% CI: 0.14 to 1.73; I^2 = N/A	IMRT: 6.67% (4/60) vs. 3DCRT: 13.64% (6/44)	1 Observational study,[47] 104 patients.
Multi-modalities compared with IORT	Breast edema	Acute	IRR: 0.81; 95% CI: 0.36 to 1.85; I^2 = N/A	Multi-modalities: 3.33% (10/300) vs. IORT: 4.11% (13/316)	1 Observational study,[45] 616 patients.
	General	Acute	IRR: 0.36; 95% CI: 0.22 to 0.58; I^2 = N/A	Multi-modalities: 7.33% (22/300) vs. IORT: 20.57% (65/316)	1 Observational study,[45] 616 patients.
	Pain	Acute	IRR: 1.08; 95% CI: 0.71 to 1.62; I^2 = N/A	Multi-modalities: 15.33% (46/300) vs. IORT: 14.24% (45/316)	1 Observational study,[45] 616 patients.
	Skin	Acute	IRR: 1.32; 95% CI: 0.52 to 3.34; I^2 = N/A	Multi-modalities: 3.33% (10/300) vs. IORT: 2.53% (8/316)	1 Observational study,[45] 616 patients.
	Wound	Acute	IRR: 0.40; 95% CI: 0.22 to 0.74; I^2 = N/A	Multi-modalities: 4.67% (14/300) vs. IORT: 11.71% (37/316)	1 Observational study,[45] 616 patients.

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
Multi-catheter interstitial brachytherapy compared with 3DCRT	Breast induration or fibrosis	Late	IRR: 2.20; 95% CI: 1.07 to 4.51; I^2 = N/A	Multi-catheter interstitial brachytherapy: 49.43% (43/87) vs. 3DCRT: 22.5% (9/40)	1 RCT,[1-5] 127 patients.
	Skin	Late	IRR: 0.27; 95% CI: 0.12 to 0.59; I^2 = N/A	Multi-catheter interstitial brachytherapy: 11.49% (10/87) vs. 3DCRT: 42.5% (17/40)	1 RCT,[1] 127 patients.
	Soft tissue	Late	IRR: 2.10; 95% CI: 0.93 to 4.76; I^2 = N/A	Multi-catheter interstitial brachytherapy: 36.78% (32/87) vs. 3DCRT: 17.5% (7/40)	1 RCT,[1] 127 patients.
Proton compared with 3DCRT	Skin	Late	IRR: 10.39; 95% CI: 3.26 to 33.14; I^2 = N/A	Proton: 52.63% (10/19) vs. 3DCRT: 5.06% (4/79)	1 Observational study,[41] 98 patients.
	Soft tissue	Late	IRR: 0.83; 95% CI: 0.18 to 3.80; I^2 = N/A	Proton: 10.53% (2/19) vs. 3DCRT: 12.66% (10/79)	1 Observational study,[41] 98 patients.
	Telangiectasia	Late	IRR: 9.70; 95% CI: 2.51 to 37.52; I^2 = N/A	Proton: 36.84% (7/19) vs. 3DCRT: 3.80% (3/79)	1 Observational study,[41] 98 patients.
Single-catheter brachytherapy compared with 3DCRT	Breast edema	Late	IRR: 0.35; 95% CI: 0.13 to 0.95; I^2 = N/A	Single-catheter brachytherapy: 5.95% (15/252) vs. 3DCRT: 17.24% (5/29)	1 Observational study,[52] 281 patients.
	Breast induration or fibrosis	Late	IRR: 1.50; 95% CI: 0.87 to 2.59; I^2 = N/A	Single-catheter brachytherapy: 72.62% (183/252) vs. 3DCRT: 48.28% (14/29)	1 Observational study,[52] 281 patients.
	Pain	Late	IRR: 0.78; 95% CI: 0.47 to 1.30; I^2 = N/A	Single-catheter brachytherapy: 45.63% (115/252) vs. 3DCRT: 58.62% (17/29)	1 Observational study,[52] 281 patients.
	Skin	Acute	IRR: 1.02; 95% CI: 0.61 to 1.71; I^2 = N/A	Single-catheter brachytherapy: 56.35% (142/252) vs. 3DCRT: 55.17% (16/29)	1 Observational study,[52] 281 patients.
	Skin	Late	IRR: 1.12; 95% CI: 0.70 to 1.77; I^2 = N/A	Single-catheter brachytherapy: 76.98% (194/252) vs. 3DCRT: 68.97% (20/29)	1 Observational study,[52] 281 patients.

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
Single-catheter brachytherapy compared with 3DCRT (continued)	Soft tissue	Late	IRR: 80.56; 95% CI: 0 to +∞; I^2 = N/A	Single-catheter brachytherapy: 2.78% (7/252) vs. 3DCRT: 0.03% (0.01/29)	1 Observational study,[52] 281 patients.
	Telangiectasia	Late	IRR: 0.82; 95% CI: 0.37 to 1.81; I^2 = N/A	Single-catheter brachytherapy: 19.84% (50/252) vs. 3DCRT: 24.14% (7/29)	1 Observational study,[52] 281 patients.
	Wound	Late	IRR: 6.69; 95% CI: 2.14 to 20.91; I^2 = N/A	Single-catheter brachytherapy: 69.44% (175/252) vs. 3DCRT: 10.38% (3.01/29)	1 Observational study,[52] 281 patients.
Single-catheter brachytherapy compared with multi-catheter interstitial brachytherapy	Breast induration or fibrosis	Late	IRR: 0.33; 95% CI: 0.10 to 1.11; I^2 = N/A	Single-catheter brachytherapy: 10.71% (3/28) vs. multi-catheter interstitial brachytherapy: 132% (24/75)	1 Observational study,[50] 103 patients.
	Skin	Late	IRR: 1.89; 95% CI: 0.90 to 3.96; I^2 = N/A	Single-catheter brachytherapy: 42.86% (12/28) vs. multi-catheter interstitial brachytherapy: 22.67% (17/75)	1 Observational study,[50] 103 patients.
	Soft tissue	Late	IRR: 0.60; 95% CI: 0.13 to 2.75; I^2 = N/A	Single-catheter brachytherapy: 7.14% (2/28) vs. multi-catheter interstitial brachytherapy: 12% (9/75)	1 Observational study,[50] 103 patients.

Abbreviations: ∞ = infinity; 3DCRT = 3-dimensional conformal external beam radiation therapy; CI = confidence interval; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; IRR = incidence rate ratio; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial

Table I.3. KQ 1. Adverse events by grade

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
PBI compared with WBI	AE grade 1	Acute	IRR: 0.86; 95% CI: 0.32 to 2.32; I^2 = 86.81%	PBI: 49.66% (553/1113) vs. WBI: 51.62% (589/1141)	5 RCTs,[9-18, 25, 38] 2254 patients.
	AE grade 2	Acute	IRR: 0.23; 95% CI: 0.08 to 0.61; I^2 = 91.96%	PBI: 15.62% (341/2183) vs. WBI: 37.22% (821/2206)	6 RCTs,[9-18, 22-25, 38] 4389 patients.
	AE grade 3	Acute	IRR: 0.36; 95% CI: 0 to 47.94; I^2 = 86.21%	PBI: 1.23% (22/1790) vs. WBI: 3.27% (59/1805)	3 RCTs,[14-17, 22-24, 38] 3595 patients.
	AE grade 1	Late	IRR: 0.71; 95% CI: 0.32 to 1.58; I^2 = 92.91%	PBI: 43.29% (1394/3220) vs. WBI: 39.45% (1282/3250)	6 RCTs,[9-19, 25, 38] 6470 patients.
	AE grade 2	Late	IRR: 0.75; 95% CI: 0.28 to 2.00; I^2 = 95.15%	PBI: 32.23% (1299/4030) vs. WBI: 35.29% (1431/4055)	6 RCTs,[14-19, 22-25, 38] 8085 patients.
	AE grade 3	Late	IRR: 1.20; 95% CI: 0.03 to 44.79; I^2 = 91.23%	PBI: 6.60% (253/3832) vs. WBI: 4.50% (173/3847)	3 RCTs,[14-17, 19, 22-24] 7679 patients.
	AE grade 4	Late	IRR: 1.67; 95% CI: 0.61 to 4.59; I^2 = N/A	PBI: 0.47% (10/2107) vs. WBI: 0.28% (6/2109)	1 RCT,[19] 4216 patients.
3DCRT compared with WBI	AE grade 1	Acute	IRR: 1.58; 95% CI: 0.00 to +∞; I^2 = 84.46%	3DCRT: 45.69% (53/116) vs. WBI: 27.12% (32/118)	2 RCTs,[25, 38] 234 patients.
	AE grade 2	Acute	IRR: 0.47; 95% CI: 0.15 to 1.44; I^2 = 50.48%	3DCRT: 24.79% (294/1186) vs. WBI: 42,86% (507/1183)	3 RCTs,[22-26, 38] 2369 patients.
	AE grade 3	Acute	IRR: 1.05; 95% CI: 0.02 to 61.50; I^2 = 0%	3DCRT: 1.76% (20/1135) vs. WBI: 1.68% (19/1132)	2 RCTs, [22-24, 38] 2267 patients.
	AE grade 1	Late	IRR: 0.82; 95% CI: 0.01 to 59.00; I^2 = 73.08%	3DCRT: 62.93% (73/116) vs. WBI: 87.29% (103/118)	2 RCTs,[25, 38] 234 patients.
	AE grade 2	Late	IRR: 0.55; 95% CI: 0.01 to 38.86; I^2 = 93.28%	3DCRT: 25.72% (305/1186) vs. WBI: 13.86% (164/1183)	3 RCTs,[22-26, 38] 2369 patients.
	AE grade 3	Late	IRR: 4.34; 95% CI: 2.26 to 8.36; I^2 = N/A	3DCRT: 4.49% (48/1070) vs. WBI: 1.03% (11/1065)	1 RCT,[22-24] 2135 patients.
IMRT compared with WBI	AE grade 1	Acute	IRR: 0.44; 95% CI: 0.00 to 79.44; I^2 = 76.60%	IMRT: 16.67% (57/342) vs, WBI: 32.86% (115/350)	2 RCTs,[9-13, 18] 692 patients.
	AE grade 2	Acute	IRR: 0.06; 95% CI: 0.00 to 13.17; I^2 = 0%	IMRT: 1.75% (6/342) vs, WBI: 27.71% (97/350)	2 RCTs,[9-13, 18] 692 patients.
	AE grade 1	Late	IRR: 0.27; 95% CI: 0.00 to 292.36; I^2 = 82.93%	IMRT: 7.31% (25/342) vs, WBI: 29.71% (104/350)	2 RCTs,[9-13, 18] 692 patients.
	AE grade 2	Late	IRR: 0.27; 95% CI: 0.03 to 2.45; I^2 = N/A	IMRT: 1.22% (1/82) vs, WBI: 4.44% (4/90)	1 RCT,[18] 172 patients.

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
IORT compared with WBI	AE grade 3	Late	IRR: 0.26; 95% CI: 0.11 to 0.64; I^2 = N/A	IORT: 0.35% (6/1721) vs. WBI: 1.33% (23/1730)	1 RCT,[28-37] 3451 patients.
Multi-catheter interstitial brachytherapy compared with WBI	AE grade 1	Acute	IRR: 1.03; 95% CI: 0.90 to 1.17; I^2 = N/A	Multi-catheter interstitial brachytherapy: 67.63% (443/655) vs, WBI: 29.75% (442/673)	1 RCT,[14-17] 1328 patients.
	AE grade 2	Acute	IRR: 0.19; 95% CI: 0.14 to 0.27; I^2 = N/A	Multi-catheter interstitial brachytherapy: 6.26% (41/655) vs. WBI: 32.24% (217/673)	1 RCT,[14-17] 1328 patients.
	AE grade 3	Acute	IRR: 0.05; 95% CI: 0.01 to 0.21; I^2 = N/A	Multi-catheter interstitial brachytherapy: 0.31% (2/655) vs. WBI: 5.94% (40/673)	1 RCT,[14-17] 1328 patients.
	AE grade 1	Late	IRR: 1.03; 95% CI: 0.91 to 1.18; I^2 = N/A	Multi-catheter interstitial brachytherapy: 68.85% (451/655) vs. WBI: 66.72% (449/673)	1 RCT,[14-17] 1328 patients.
	AE grade 2	Late	IRR: 1.06; 95% CI: 0.76 to 1.47; I^2 = N/A	Multi-catheter interstitial brachytherapy: 10.99% (72/655) vs. WBI: 10.40% (70/673)	1 RCT,[14-17] 1328 patients.
	AE grade 3	Late	IRR: 0.22; 95% CI: 0.07 to 0.64; I^2 = N/A	Multi-catheter interstitial brachytherapy: 0.61% (4/655) vs. WBI: 2.82% (19/673)	1 RCT,[14-17] 1328 patients.

Comparison	Outcome	Time	Findings	Percentage (Events/Patients)	Study Design and Sample Size
Multi-modalities compared with WBI	AE grade 1	Late	IRR: 1.35; 95% CI: 1.22 to 1.50; I^2 = N/A	Multi-modalities: 40.10% (845/2107) vs. WBI: 29.68% (626/2109)	1 RCT,[19] 4216 patients.
	AE grade 2	Late	IRR: 0.77; 95% CI: 0.71 to 0.84; I^2 = N/A	Multi-modalities: 43.71% (921/2107) vs. WBI: 56.57% (1193/2109)	1 RCT,[19] 4216 patients.
	AE grade 3	Late	IRR: 1.41; 95% CI: 1.14 to 1.74; I^2 = N/A	Multi-modalities: 9.54% (201/2107) vs. WBI: 6.78% (143/2109)	1 RCT,[19] 4216 patients.
	AE grade 4	Late	IRR: 1.67; 95% CI: 0.61 to 4.59; I^2 = N/A	Multi-modalities: 0.47% (10/2107) vs. WBI: 0.28% (6/2109)	1 RCT,[19] 4216 patients.

Abbreviations: ∞ = infinity; 3DCRT: 3-dimensional conformal external beam radiation therapy; AE = adverse event; CI: confidence interval; IMRT: intensity modulated radiation therapy; IORT: intraoperative radiotherapy; IRR: incidence rate ratio; KQ = Key Question; N/A: not applicable; PBI: partial breast irradiation; RCT = randomized clinical trial; WBI: whole breast irradiation

Table I.4. KQ 2. Adverse events by grade

Comparison	Outcome	Timing	Findings	Percentage (Events/Patients)	Study Design and Sample Size
IMRT compared with 3DCRT	AE grade 1	Acute	IRR: 0.5; 95% CI: 0.35 to 0.72; I^2 = N/A	IMRT: 83.33% (50/60) vs. 3DCRT: 165.91% (73/44)	1 Observational study,[47] 104 patients.
	AE grade 1	Late	IRR: 0.52; 95% CI: 0.31 to 0.87; I^2 = N/A	IMRT: 40% (24/60) vs. 3DCRT: 77.27% (34/44)	1 Observational study,[47] 104 patients.
Multi-modalities compared with IORT	AE grade 2	Acute	IRR: 0.39; 95% CI: 0.16 to 0.92; I^2 = N/A	Multi-modalities: 2.33% (7/300) vs. IORT: 6.01% (19/316)	1 Observational study,[42] 616 patients.
	AE grade 3	Acute	IRR: 0.35; 95% CI: 0.10 to 1.30; I^2 = N/A	Multi-modalities: 1% (3/300) vs. IORT: 2.85% (9/316)	1 Observational study,[42] 616 patients.
Single-catheter brachytherapy compared with 3DCRT	AE grade 1	Acute	IRR: 0.95; 95% CI: 0.53 to 1.68; I^2 = N/A	Single-catheter brachytherapy: 42.46% (107/252) vs. 3DCRT: 44.83% (13/)29	1 Observational study,[52] 281 patients.
	AE grade 2	Acute	IRR: 1.90; 95% CI: 0.46 to 7.91; I^2 = N/A	Single-catheter brachytherapy: 13.10% (33/252) vs. 3DCRT: 6.90% (2/29)	1 Observational study,[52] 281 patients.
	AE grade 3	Acute	IRR: 0.23; 95% CI: 0.02 to 2.54; I^2 = N/A	Single-catheter brachytherapy: 0.79% (2/)252 vs. 3DCRT: 3.45% (1/29)	1 Observational study,[52] 281 patients.
	AE grade 1	Late	IRR: 0.90; 95% CI: 0.56 to 1.43; I^2 = N/A	Single-catheter brachytherapy: 61.90% (156/252) vs. 3DCRT: 68.97% (20/29)	1 Observational study,[52] 281 patients.
	AE grade 2	Late	IRR: 1.63; 95% CI: 0.66 to 4.05; I^2 = N/A	Single-catheter brachytherapy: 28.17% (71/252) vs. 3DCRT: 17.24% (5/29)	1 Observational study,[52] 281 patients.
	AE grade 3	Late	IRR: 1.09; 95% CI: 0.25 to 4.69; I^2 = N/A	Single-catheter brachytherapy: 7.54% (19/252) vs. 3DCRT: 6.90% (2/29)	1 Observational study,[52] 281 patients.

Abbreviations: 3DCRT: 3-dimensional conformal external beam radiation therapy; AE = adverse event; CI: confidence interval; IMRT: intensity modulated radiation therapy; IORT: intraoperative radiotherapy; IRR: incidence rate ratio; KQ = Key Question; N/A: not applicable

Appendix J. Subgroup Analysis

Table J.1. Subgroup analyses. KQ 1: Age

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI 3DCRT vs. WBI	Age	<50 years	IBR	10 years	HR: 0.78; 95% CI: 0.29 to 2.11; I^2 = N/A	N/A	1 RCT[22-24]
	Age	≥50 years	IBR	10 years	HR: 1.44; 95% CI: 0.91 to 2.27; I^2 = N/A	N/A	1 RCT[22-24]
APBI IMRT vs. WBI	Age	<50 years	IBR	5 years	RR: 1.10; 95% CI: 0.07 to 16.99; I^2 = N/A	APBI IMRT: 2.44% (1/41) vs. WBI: 2.22% (1/45)	1 RCT[9-13]
	Age	51-59 years	IBR	5 years	RR: 3.73; 95% CI: 0.15 to 89.87; I^2 = N/A	APBI IMRT: 1.64% (1/61) vs. WBI: 0% (0/76)	1 RCT[9-13]
	Age	60-69 years	IBR	5 years	RR: 0.27; 95% CI: 0.01 to 6.62; I^2 = N/A	APBI IMRT: 0% (0/99) vs. WBI: 1.23% (1/81)	1 RCT[9-13]
	Age	≥70 years	IBR	5 years	RR: 0.98; 95% CI: 0.06 to 15.35; I^2 = N/A	APBI IMRT: 1.69% (1/59) vs. WBI: 1.72% (1/58)	1 RCT[9-13]
APBI IORT vs. WBI	Age	<60 years	IBR	>10 years	RR: 4.70; 95% CI: 2.12 to 10.42; I^2 = N/A	APBI IORT: 10.61% (35/330) vs. WBI: 2.26% (7/310)	1 RCT[7, 8]
	Age	60-69 years	IBR	>10 years	RR: 5.37; 95% CI: 2.28 to 12.65; I^2 = N/A	APBI IORT: 11.97% (31/259) vs. WBI: 2.23% (6/269)	1 RCT[7, 8]
	Age	≥70 years	IBR	>10 years	RR: 1.61; 95% CI: 0.38 to 6.94; I^2 = N/A	APBI IORT: 6.45% (4/62) vs. WBI: 4% (3/75)	1 RCT[7, 8]
	Age	<60 years	IBR	>10 years	HR: 4.82; 95% CI: 2.14 to 10.86; I^2 = N/A	APBI IORT: 10.61% (35/330) vs. WBI: 2.26% (7/310)	1 RCT[7, 8]
	Age	60-69 years	IBR	>10 years	HR: 5.69; 95% CI: 2.37 to 13.64; I^2 = N/A	APBI IORT: 11.97% (31/259) vs. WBI: 2.23% (6/269)	1 RCT[7, 8]
	Age	≥70 years	IBR	>10 years	HR: 1.86; 95% CI: 0.41 to 8.33; I^2 = N/A	APBI IORT: 6.45% (4/62) vs. WBI: 4% (3/75)	1 RCT[7, 8]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.2. Subgroup analyses. KQ 1: Accelerated partial breast irradiation suitability

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI vs. WBI	APBI suitability	No	IBR	10 years	HR: 1.34; 95% CI: 0.12 to 15.15; I^2 = 0%	N/A	2 RCTs[19, 22-24]
	APBI suitability	Yes	IBR	10 years	HR: 1.08; 95% CI: 0.04 to 28.87; I^2 = 0%	N/A	2 RCTs[19, 22-24]
APBI 3DCRT vs. WBI	APBI suitability	No	IBR	10 years	HR: 1.46; 95% CI: 0.83 to 2.58; I^2 = N/A	N/A	1 RCT[22-24]
	APBI suitability	Yes	IBR	10 years	HR: 1.06; 95% CI: 0.57 to 1.95; I^2 = N/A	N/A	1 RCT[22-24]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; WBI = whole breast irradiation

Table J.3. Subgroup analyses. KQ 1: Adjuvant therapy

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI 3DCRT vs. WBI	Adjuvant therapy	No	IBR	10 years	HR: 1.23; 95% CI: 0.55 to 2.73; I^2 = N/A	N/A	1 RCT[22-24]
	Adjuvant therapy	Yes	IBR	10 years	HR: 1.08; 95% CI: 0.58 to 2.00; I^2 = N/A	N/A	1 RCT[22-24]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; WBI = whole breast irradiation

Table J.4. Subgroup analyses. KQ 1: Disease stage

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI vs. WBI	Disease stage	DCIS only	IBR	10 years	HR: 1.26; 95% CI: 0.04 to 45.14; I^2 = 35.10%	N/A	2 RCTs[19, 22-24]
	Disease stage	Invasive disease	IBR	10 years	HR: 1.21; 95% CI: 0.06 to 22.96; I^2 = 0%	N/A	2 RCTs[19, 22-24]
APBI 3DCRT vs. WBI	Disease stage	DCIS only	IBR	10 years	HR: 1.81; 95% CI: 0.84 to 3.91; I^2 = N/A	N/A	1 RCT[22-24]
	Disease stage	Invasive disease	IBR	10 years	HR: 1.12; 95% CI: 0.69 to 1.84; I^2 = N/A	N/A	1 RCT[22-24]
APBI IMRT vs. WBI	Disease stage	pTis	IBR	5 years	RR: 1.38; 95% CI: 0.03 to 66.88; I^2 = N/A	APBI IMRT: 0% (0/23) vs. WBI: 0% (0/32)	1 RCT[9-13]
	Disease stage	pT1a	IBR	5 years	RR: 0.22; 95% CI: 0.01 to 5.09; I^2 = N/A	APBI IMRT: 0% (0/28) vs. WBI: 5.56% (1/18)	1 RCT[9-13]
	Disease stage	pT1b	IBR	5 years	RR: 4.49; 95% CI: 0.22 to 92.37; I^2 = N/A	APBI IMRT: 2.04% (2/98) vs. WBI: 0% (0/88)	1 RCT[9-13]
	Disease stage	pT1c	IBR	5 years	RR: 1.10; 95% CI: 0.07 to 17.4; I^2 = N/A	APBI IMRT: 1.03% (1/97) vs. WBI: 0.93% (1/107)	1 RCT[9-13]
	Disease stage	pT2	IBR	5 years	RR: 0.36; 95% CI: 0.02 to 8.07; I^2 = N/A	APBI IMRT: 0% (0/14) vs. WBI: 6.67% (1/15)	1 RCT[9-13]
APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT vs. WBI	Disease stage	DCIS only	IBR	10 years	RR: 1.07; 95% CI: 0.66 to 1.74; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 6.23% (32/514) vs. WBI: 5.82% (29/498)	1 RCT[19]
	Disease stage	Noninvasive disease	IBR	10 years	RR: 1.29; 95% CI: 0.85 to 1.95; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 3.68% (50/1359) vs. WBI: 2.86% (38/1330)	1 RCT[19]
	Disease stage	Invasive disease	IBR	10 years	RR: 1.93; 95% CI: 0.59 to 6.30; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 3.70% (8/216) vs. WBI: 1.92% (4/208)	1 RCT[19]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT vs. WBI (continued)	Disease stage	DCIS only	IBR	10 years	HR: 1.01; 95% CI: 0.61 to 1.68; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 6.23% (32/514) vs. WBI: 5.82% (29/498)	1 RCT[19]
	Disease stage	Noninvasive disease	IBR	10 years	HR: 1.31; 95% CI: 0.85 to 2.00; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 3.68% (50/1359) vs. WBI: 2.86% (38/1330)	1 RCT[19]
	Disease stage	Invasive disease	IBR	10 years	HR: 1.91; 95% CI: 0.57 to 6.34; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 3.70% (8/216) vs. WBI: 1.92% (4/208)	1 RCT[19]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; DCIS = ductal carcinoma in situ; HR = hazard ratio; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.5. Subgroup analyses. KQ 1: Estrogen receptor status

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI vs. WBI	ER status	Negative	IBR	10 years	HR: 0.99; 95% CI: 0.03 to 29.08; I^2 = 0%	N/A	2 RCTs[19, 22-24]
	ER status	Positive	IBR	10 years	HR: 1.28; 95% CI: 0.17 to 9.46; I^2 = 0%	N/A	2 RCTs[19, 22-24]
APBI 3DCRT vs. WBI	ER status	Negative	IBR	10 years	HR: 1.01; 95% CI: 0.34 to 3.04; I^2 = N/A	N/A	1 RCT[22-24]
	ER status	Positive	IBR	10 years	HR: 1.19; 95% CI: 0.69 to 2.07; I^2 = N/A	N/A	1 RCT[22-24]
APBI IMRT vs. WBI	ER status	Negative	IBR	5 years	RR: 0.31; 95% CI: 0.01 to 6.85; I^2 = N/A	APBI IMRT: 0% (0/12) vs. WBI: 9.09% (1/11)	1 RCT[9-13]
	ER status	Positive	IBR	5 years	RR: 1.51; 95% CI: 0.25 to 8.94; I^2 = N/A	APBI IMRT: 1.21% (3/248) vs. WBI: 0.80% (2/249)	1 RCT[9-13]
APBI IORT vs. WBI	ER status	Negative	IBR	>10 years	RR: 9.78; 95% CI: 1.30 to 73.36; I^2 = N/A	APBI IORT: 17.46% (11/63) vs. WBI: 1.79% (1/56)	1 RCT[7, 8]
	ER status	Positive	IBR	>10 years	RR: 3.97; 95% CI: 2.28 to 6.92; I^2 = N/A	APBI IORT: 10.27% (50/487) vs. WBI: 2.93% (15/512)	1 RCT[7, 8]
	ER status	Negative	IBR	>10 years	HR: 9.25; 95% CI: 1.19 to 71.70; I^2 = N/A	APBI IORT: 17.46% (11/63) vs. WBI: 1.79% (1/56)	1 RCT[7, 8]
	ER status	Positive	IBR	>10 years	HR: 4.21; 95% CI: 2.39 to 7.42; I^2 = N/A	APBI IORT: 10.12% (59/583) vs. WBI: 2.55% (15/589)	1 RCT[7, 8]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
IORT during lumpectomy vs. WBI	ER status	Negative	IBR	5 years	RR: 3.68; 95% CI: 0.80 to 16.96; I^2 = N/A	IORT during lumpectomy: 7.02% (8/114) vs. WBI: 1.90% (2/105)	1 RCT[28-37]
	ER status	Positive	IBR	5 years	RR: 1.71; 95% CI: 0.75 to 3.89; I^2 = N/A	IORT during lumpectomy: 1.49% (15/1005) vs. WBI: 0.87% (9/1030)	1 RCT[28-37]
	ER status	Negative	Overall survival	5 years	RR: 1.05; 95% CI: 0.97 to 1.13; I^2 = N/A	IORT during lumpectomy: 94.74% (108/114) vs. WBI: 90.48% (95/105)	1 RCT[28-37]
	ER status	Positive	Overall survival	5 years	RR: 1.01; 95% CI: 0.99 to 1.03; I^2 = N/A	IORT during lumpectomy: 96.52% (970/1005) vs. WBI: 95.53% (984/1030)	1 RCT[28-37]
	ER status	Negative	Overall survival	>10 years	HR: 0.64; 95% CI: 0.35 to 1.18; I^2 = N/A	N/A	1 RCT[28-37]
	ER status	Positive	Overall survival	>10 years	HR: 0.82; 95% CI: 0.62 to 1.08; I^2 = N/A	N/A	1 RCT[28-37]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.6. Subgroup analyses. KQ 1: Histology

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI IORT vs. WBI	Histology	Ductal	IBR	>10 years	RR: 5.17; 95% CI: 2.75 to 9.74; I^2 = N/A	APBI IORT: 11.07% (58/524) vs. WBI: 2.14% (11/514)	1 RCT[7, 8]
	Histology	Lobular	IBR	>10 years	RR: 1.88; 95% CI: 0.58 to 6.06; I^2 = N/A	APBI IORT: 13.21% (7/53) vs. WBI: 7.02% (4/57)	1 RCT[7, 8]
	Histology	Mixed	IBR	>10 years	RR: 6.11; 95% CI: 0.31 to 119.33; I^2 = N/A	APBI IORT: 11.76% (2/17) vs. WBI: 0% (0/21)	1 RCT[7, 8]
	Histology	Other	IBR	>10 years	RR: 3.11; 95% CI: 0.33 to 29.00; I^2 = N/A	APBI IORT: 5.66% (3/53) vs. WBI: 1.82% (1/55)	1 RCT[7, 8]
	Histology	Ductal	IBR	>10 years	HR: 5.36; 95% CI: 2.81 to 10.21; I^2 = N/A	APBI IORT: 11.07% (58/524) vs. WBI: 2.14% (11/514)	1 RCT[7, 8]
	Histology	Lobular	IBR	>10 years	HR: 2.13; 95% CI: 0.62 to 7.28; I^2 = N/A	APBI IORT: 13.21% (7/53) vs. WBI: 7.02% (4/57)	1 RCT[7, 8]
	Histology	Other	IBR	>10 years	HR: 3.12; 95% CI: 0.32 to 29.96; I^2 = N/A	APBI IORT: 5.66% (3/53) vs. WBI: 1.82% (1/55)	1 RCT[7, 8]

Abbreviations: APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.7. Subgroup analyses. KQ 1: Hormone receptor status

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT vs. WBI	Hormone receptor status	ER and PR Negative	IBR	10 years	RR: 0.93; 95% CI: 0.53 to 1.65; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 5.64% (22/390) vs. WBI: 6.04% (23/381)	1 RCT[19]
	Hormone receptor status	ER Positive, PR Positive, or both	IBR	10 years	RR: 1.38; 95% CI: 0.96 to 1.98; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 4% (68/1699) vs. WBI: 2.90% (48/1655)	1 RCT[19]
	Hormone receptor status	ER and PR Negative	IBR	10 years	HR: 0.98; 95% CI: 0.54 to 1.77; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 5.64% (22/390) vs. WBI: 6.04% (23/381)	1 RCT[19]
	Hormone receptor status	ER Positive, PR Positive, or both	IBR	10 years	HR: 1.32; 95% CI: 0.91 to 1.92; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 4% (68/1699) vs. WBI: 2.90% (48/1655)	1 RCT[19]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IBR = ipsilateral breast recurrence; KQ = Key Question; N/A = not applicable; PR = progesterone receptor; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.8. Subgroup analyses. KQ 1: Human epidermal growth factor receptor 2 status

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI IMRT vs. WBI	HER2 status	Negative	IBR	5 years	RR: 1.40; 95% CI: 0.24 to 8.28; I^2 = N/A	APBI IMRT: 1.29% (3/232) vs. WBI: 0.93% (2/216)	1 RCT[9-13]
	HER2 status	Positive	IBR	5 years	RR: 0.67; 95% CI: 0.03 to 14.35; I^2 = N/A	APBI IMRT: 0% (0/6) vs. WBI: 7.69% (1/13)	1 RCT[9-13]
APBI IORT vs. WBI	HER2 status	Negative	IBR	>10 years	RR: 4.11; 95% CI: 2.36 to 7.13; I^2 = N/A	APBI IORT: 10.53% (62/589) vs. WBI: 2.56% (15/585)	1 RCT[7, 8]
	HER2 status	Positive	IBR	>10 years	RR: 8.70; 95% CI: 1.12 to 67.43; I^2 = N/A	APBI IORT: 14.04% (8/57) vs. WBI: 1.61% (1/62)	1 RCT[7, 8]
	HER2 status	Negative	IBR	>10 years	HR: 4.35; 95% CI: 2.47 to 7.64; I^2 = N/A	APBI IORT: 10.53% (62/589) vs. WBI: 2.56% (15/585)	1 RCT[7, 8]
	HER2 status	Positive	IBR	>10 years	HR: 8.28; 95% CI: 1.04 to 66.19; I^2 = N/A	APBI IORT: 14.04% (8/57) vs. WBI: 1.61% (1/62)	1 RCT[7, 8]
IORT during lumpectomy vs. WBI	HER2 status	Negative	IBR	5 years	RR: 1.05; 95% CI: 0.22 to 5.13; I^2 = N/A	IORT during lumpectomy: 1.92% (3/156) vs. WBI: 1.83% (3/164)	1 RCT[28-37]
	HER2 status	Positive	IBR	5 years	RR: 2.39; 95% CI: 1.05 to 5.43; I^2 = N/A	IORT during lumpectomy: 2.07% (19/920) vs. WBI: 0.86% (8/925)	1 RCT[28-37]
	HER2 status	Negative	Overall survival	5 years	RR: 1.07; 95% CI: 1.00 to 1.13; I^2 = N/A	IORT during lumpectomy: 96.15% (150/156) vs. WBI: 90.24% (148/164)	1 RCT[28-37]
	HER2 status	Positive	Overall survival	5 years	RR: 1.00; 95% CI: 0.99 to 1.02; I^2 = N/A	IORT during lumpectomy: 96.20% (885/920) vs. WBI: 95.78% (886/925)	1 RCT[28-37]
	HER2 status	Negative	Overall survival	>10 years	HR: 0.85; 95% CI: 0.64 to 1.14; I^2 = N/A	N/A	1 RCT[28-37]
	HER2 status	Positive	Overall survival	>10 years	HR: 0.91; 95% CI: 0.52 to 1.61; I^2 = N/A	N/A	1 RCT[28-37]

Abbreviations: APBI = accelerated partial breast irradiation; CI = confidence interval; HER2 = Human Epidermal Growth Factor Receptor 2; HR = hazard ratio; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.9. Subgroup analyses. KQ 1: Intent to receive chemotherapy

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT vs. WBI	Intent to receive chemotherapy	No	IBR	10 years	RR: 1.15; 95% CI: 0.81 to 1.63; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 4.44% (66/1487) vs. WBI: 3.86% (56/1449)	1 RCT[19]
	Intent to receive chemotherapy	Yes	IBR	10 years	RR: 1.56; 95% CI: 0.83 to 2.94; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 3.99% (24/602) vs. WBI: 2.56% (15/587)	1 RCT[19]
	Intent to receive chemotherapy	No	IBR	10 years	HR: 1.14; 95% CI: 0.80 to 1.63; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 4.44% (66/1487) vs. WBI: 3.86% (56/1449)	1 RCT[19]
	Intent to receive chemotherapy	Yes	IBR	10 years	HR: 1.51; 95% CI: 0.79 to 2.88; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 3.99% (24/602) vs. WBI: 2.56% (15/587)	1 RCT[19]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.10. Subgroup analyses. KQ 1: Invasive cancer risk group

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT vs. WBI	Invasive cancer risk group	Low-risk invasive	IBR	10 years	RR: 1.13; 95% CI: 0.47 to 2.76; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 2.66% (10/376) vs. WBI: 2.34% (9/384)	1 RCT[19]
	Invasive cancer risk group	All other invasive	IBR	10 years	RR: 1.28; 95% CI: 0.79 to 2.08; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 3.61% (37/1025) vs. WBI: 2.82% (28/993)	1 RCT[19]
	Invasive cancer risk group	Low-risk invasive	IBR	10 years	HR: 1.12; 95% CI: 0.46 to 2.76; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 2.66% (10/376) vs. WBI: 2.34% (9/384)	1 RCT[19]
	Invasive cancer risk group	All other invasive	IBR	10 years	HR: 1.26; 95% CI: 0.77 to 2.08; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 3.61% (37/1025) vs. WBI: 2.82% (28/993)	1 RCT[19]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.11. Subgroup analyses. KQ 1: Ki-67 proliferative index

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI IMRT vs. WBI	Ki-67 proliferative index	<20%	IBR	5 years	RR: 2.70; 95% CI: 0.28 to 25.76; I^2 = N/A	APBI IMRT: 1.55% (3/193) vs. WBI: 0.57% (1/174)	1 RCT[9-13]
	Ki-67 proliferative index	≥20%	IBR	5 years	RR: 0.27; 95% CI: 0.01 to 5.43; I^2 = N/A	APBI IMRT: 0% (0/50) vs. WBI: 2.99% (2/67)	1 RCT[9-13]
APBI IORT vs. WBI	Ki-67 proliferative index	<14%	IBR	>10 years	RR: 2.37; 95% CI: 1.01 to 5.57; I^2 = N/A	APBI IORT: 6.84% (18/263) vs. WBI: 2.89% (7/242)	1 RCT[7, 8]
	Ki-67 proliferative index	14-20%	IBR	>10 years	RR: 29; 95% CI: 1.75 to 481.39; I^2 = N/A	APBI IORT: 10.14% (14/138) vs. WBI: 0% (0/138)	1 RCT[7, 8]
	Ki-67 proliferative index	>20%	IBR	>10 years	RR: 4.59; 95% CI: 2.26 to 9.28; I^2 = N/A	APBI IORT: 15.57% (38/244) vs. WBI: 3.40% (9/265)	1 RCT[7, 8]
	Ki-67 proliferative index	<14%	IBR	>10 years	HR: 2.50; 95% CI: 1.04 to 5.99; I^2 = N/A	APBI IORT: 6.84% (18/263) vs. WBI: 2.89% (7/242)	1 RCT[7, 8]
	Ki-67 proliferative index	>20%	IBR	>10 years	HR: 4.89; 95% CI: 2.36 to 10.11; I^2 = N/A	APBI IORT: 15.57% (38/244) vs. WBI: 3.40% (9/265)	1 RCT[7, 8]

Abbreviations: APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.12. Subgroup analyses. KQ 1: Lymph node status

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
IORT during lumpectomy vs. WBI	Lymph node status	Negative	IBR	5 years	RR: 2.28; 95% CI: 1.04 to 4.97; I^2 = N/A	IORT during lumpectomy: 2.29% (20/872) vs. WBI: 1.01% (9/893)	1 RCT[28-37]
	Lymph node status	Positive	IBR	5 years	RR: 1.84; 95% CI: 0.34 to 9.97; I^2 = N/A	IORT during lumpectomy: 1.57% (4/254) vs. WBI: 0.85% (2/234)	1 RCT[28-37]
	Lymph node status	Negative	Overall survival	5 years	RR: 1.02; 95% CI: 1.00 to 1.04; I^2 = N/A	IORT during lumpectomy: 96.90% (845/872) vs. WBI: 95.30% (851/893)	1 RCT[28-37]
	Lymph node status	Positive	Overall survival	5 years	RR: 1.00; 95% CI: 0.96 to 1.05; I^2 = N/A	IORT during lumpectomy: 94.09% (239/254) vs. WBI: 94.02% (220/234)	1 RCT[28-37]
	Lymph node status	Negative	Overall survival	>10 years	HR: 0.80; 95% CI: 0.60 to 1.08; I^2 = N/A	N/A	1 RCT[28-37]
	Lymph node status	Positive	Overall survival	>10 years	HR: 0.84; 95% CI: 0.51 to 1.39; I^2 = N/A	N/A	1 RCT[28-37]

Abbreviations: CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.13. Subgroup analyses. KQ 1: Lymphvascular invasion

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI IMRT vs. WBI	Lymphovascular invasion	Absence	IBR	5 years	RR: 0.95; 95% CI: 0.19 to 4.66; I^2 = N/A	APBI IMRT: 1.24% (3/241) vs. WBI: 1.31% (3/229)	1 RCT[9-13]
	Lymphovascular invasion	Presence	IBR	5 years	RR: 1.60; 95% CI: 0.03 to 77.47; I^2 = N/A	APBI IMRT: 0% (0/19) vs. WBI: 0% (0/31)	1 RCT[9-13]

Abbreviations: APBI = accelerated partial breast irradiation; CI = confidence interval; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.14. Subgroup analyses. KQ 1: Menopausal status

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT vs. WBI	Menopausal status	Premenopausal	IBR	10 years	RR: 1.51; 95% CI: 0.97 to 2.37; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 5.82% (47/808) vs. WBI: 3.85% (30/780)	1 RCT[19]
	Menopausal status	Postmenopausal	IBR	10 years	RR: 1.03; 95% CI: 0.68 to 1.57; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 3.36% (43/1281) vs. WBI: 3.26% (41/1256)	1 RCT[19]
	Menopausal status	Premenopausal	IBR	10 years	HR: 1.47; 95% CI: 0.93 to 2.34; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 5.82% (47/808) vs. WBI: 3.85% (30/780)	1 RCT[19]
	Menopausal status	Postmenopausal	IBR	10 years	HR: 1.03; 95% CI: 0.67 to 1.58; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 3.36% (43/1281) vs. WBI: 3.26% (41/1256)	1 RCT[19]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.15. Subgroup analyses. KQ 1: Molecular subtype

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI IORT vs. WBI	Molecular subtype	HER2 positive	IBR	>10 years	RR: 2.40; 95% CI: 0.23 to 24.57; I^2 = N/A	APBI IORT: 10% (2/20) vs. WBI: 4.17% (1/24)	1 RCT[7, 8]
	Molecular subtype	Luminal A	IBR	>10 years	RR: 2.25; 95% CI: 0.95 to 5.33; I^2 = N/A	APBI IORT: 6.64% (17/256) vs. WBI: 2.95% (7/237)	1 RCT[7, 8]
	Molecular subtype	Luminal B	IBR	>10 years	RR: 5.65; 95% CI: 2.69 to 11.86; I^2 = N/A	APBI IORT: 12.84% (42/327) vs. WBI: 2.27% (8/352)	1 RCT[7, 8]
	Molecular subtype	Triple negative	IBR	>10 years	RR: 14.25; 95% CI: 0.86 to 236.16; I^2 = N/A	APBI IORT: 20.93% (9/43) vs. WBI: 0% (0/32)	1 RCT[7, 8]
	Molecular subtype	HER2 positive	IBR	>10 years	HR: 2.15; 95% CI: 0.19 to 23.93; I^2 = N/A	APBI IORT: 10% (2/20) vs. WBI: 4.17% (1/24)	1 RCT[7, 8]
	Molecular subtype	Luminal A	IBR	>10 years	HR: 2.38; 95% CI: 0.99 to 5.74; I^2 = N/A	APBI IORT: 6.64% (17/256) vs. WBI: 2.95% (7/237)	1 RCT[7, 8]
	Molecular subtype	Luminal B	IBR	>10 years	HR: 6.00; 95% CI: 2.82 to 12.78; I^2 = N/A	APBI IORT: 12.84% (42/327) vs. WBI: 2.27% (8/352)	1 RCT[7, 8]

Abbreviations: APBI = accelerated partial breast irradiation; CI = confidence interval; HER2 = Human Epidermal Growth Factor Receptor 2; HR = hazard ratio; IBR = ipsilateral breast recurrence; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.16. Subgroup analyses. KQ 1: Number of positive nodes

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI IMRT vs. WBI	Number of positive nodes	No axillary nodal dissection	IBR	5 years	RR: 1.50; 95% CI: 0.03 to 69.61; I^2 = N/A	APBI IMRT: 0% (0/9) vs. WBI: 0% (0/14)	1 RCT[9-13]
	Number of positive nodes	0	IBR	5 years	RR: 0.92; 95% CI: 0.13 to 6.46; I^2 = N/A	APBI IMRT: 0.86% (2/232) vs. WBI: 0.94% (2/213)	1 RCT[9-13]
	Number of positive nodes	1-3	IBR	5 years	RR: 5.10; 95% CI: 0.22 to 119.32; I^2 = N/A	APBI IMRT: 5.26% (1/19) vs. WBI: 0% (0/33)	1 RCT[9-13]
APBI IORT vs. WBI	Number of positive nodes	None	IBR	>10 years	RR: 5.04; 95% CI: 2.49 to 10.17; I^2 = N/A	APBI IORT: 9.62% (46/478) vs. WBI: 1.91% (9/471)	1 RCT[7, 8]
	Number of positive nodes	1-4	IBR	>10 years	RR: 3.60; 95% CI: 1.38 to 9.42; I^2 = N/A	APBI IORT: 13.04% (18/138) vs. WBI: 3.62% (5/138)	1 RCT[7, 8]
	Number of positive nodes	≥4	IBR	>10 years	RR: 3.68; 95% CI: 0.80 to 16.96; I^2 = N/A	APBI IORT: 19.35% (6/31) vs. WBI: 5.26% (2/38)	1 RCT[7, 8]
	Number of positive nodes	None	IBR	>10 years	HR: 5.47; 95% CI: 2.68 to 11.19; I^2 = N/A	APBI IORT: 9.62% (46/478) vs. WBI: 1.91% (9/471)	1 RCT[7, 8]
	Number of positive nodes	1-4	IBR	>10 years	HR: 3.49; 95% CI: 1.30 to 9.40; I^2 = N/A	APBI IORT: 13.04% (18/138) vs. WBI: 3.62% (5/138)	1 RCT[7, 8]
	Number of positive nodes	≥4	IBR	>10 years	HR: 3.21; 95% CI: 0.64 to 15.96; I^2 = N/A	APBI IORT: 19.35% (6/31) vs. WBI: 5.26% (2/38)	1 RCT[7, 8]

Abbreviations: APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.17. Subgroup analyses. KQ 1: Progesterone receptor status

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI IMRT vs. WBI	PR status	Negative	IBR	5 years	RR: 0.89; 95% CI: 0.06 to 13.54; I^2 = N/A	APBI IMRT: 3.57% (1/28) vs. WBI: 4% (1/25)	1 RCT[9-13]
	PR status	Positive	IBR	5 years	RR: 1.01; 95% CI: 0.14 to 7.13; I^2 = N/A	APBI IMRT: 0.86% (2/232) vs. WBI: 0.85% (2/235)	1 RCT[9-13]
	PR status	Negative	IBR	5 years	HR: 0.91; 95% CI: 0.06 to 14.48; I^2 = N/A	APBI IMRT: 3.57% (1/28) vs. WBI: 4% (1/25)	1 RCT[9-13]
	PR status	Positive	IBR	5 years	HR: 1.23; 95% CI: 0.17 to 8.75; I^2 = N/A	APBI IMRT: 0.86% (2/232) vs. WBI: 0.85% (2/235)	1 RCT[9-13]
APBI IORT vs. WBI	PR status	Negative	IBR	5 years	RR: 8.45; 95% CI: 1.08 to 66.20; I^2 = N/A	APBI IORT: 3.26% (9/276) vs. WBI: 0.39% (1/259)	1 RCT[28-37]
	PR status	Positive	IBR	5 years	RR: 1.30; 95% CI: 0.57 to 2.95; I^2 = N/A	APBI IORT: 1.08% (13/1204) vs. WBI: 0.83% (10/1203)	1 RCT[28-37]
	PR status	Negative	IBR	>10 years	RR: 16.71; 95% CI: 2.27 to 122.85; I^2 = N/A	APBI IORT: 12.66% (20/158) vs. WBI: 0.76% (1/132)	1 RCT[7, 8]
	PR status	Positive	IBR	>10 years	RR: 3.50; 95% CI: 1.99 to 6.16; I^2 = N/A	APBI IORT: 10.27% (50/487) vs. WBI: 2.93% (15/512)	1 RCT[7, 8]
	PR status	Negative	IBR	>10 years	HR: 17.05; 95% CI: 2.29 to 127.09; I^2 = N/A	APBI IORT: 12.66% (20/158) vs. WBI: 0.76% (1/132)	1 RCT[7, 8]
	PR status	Positive	IBR	>10 years	HR: 3.71; 95% CI: 2.08 to 6.61; I^2 = N/A	APBI IORT: 10.27% (50/487) vs. WBI: 2.93% (15/512)	1 RCT[7, 8]
	PR status	Negative	Overall survival	5 years	RR: 1.08; 95% CI: 0.49 to 2.38; I^2 = N/A	APBI IORT: 4.50% (13/289) vs. WBI: 4.14% (11/265)	1 RCT[28-37]
	PR status	Positive	Overall survival	5 years	RR: 1.01; 95% CI: 1.00 to 1.03; I^2 = N/A	APBI IORT: 98.17% (1182/1204) vs. WBI: 96.92% (1166/1203)	1 RCT[28-37]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
IORT during lumpectomy vs. WBI	PR status	Negative	IBR	5 years	RR: 4.39; 95% CI: 0.97 to 19.77; I^2 = N/A	IORT during lumpectomy: 4.55% (10/220) vs. WBI: 1.04% (2/193)	1 RCT[28-37]
	PR status	Positive	IBR	5 years	RR: 1.49; 95% CI: 0.64 to 3.46; I^2 = N/A	IORT during lumpectomy: 1.45% (13/895) vs. WBI: 0.98% (9/921)	1 RCT[28-37]
	PR status	Negative	Overall survival	5 years	RR: 1.03; 95% CI: 0.98 to 1.09; I^2 = N/A	IORT during lumpectomy: 94.55% (208/220) vs. WBI: 91.71% (177/193)	1 RCT[28-37]
	PR status	Positive	Overall survival	5 years	RR: 1.01; 95% CI: 0.99 to 1.03; I^2 = N/A	IORT during lumpectomy: 96.78% (866/895) vs. WBI: 95.66% (881/921)	1 RCT[28-37]
	PR status	Negative	Overall survival	12 years	HR: 0.77; 95% CI: 0.47 to 1.26; I^2 = N/A	N/A	1 RCT[28-37]
	PR status	Positive	Overall survival	12 years	HR: 0.78; 95% CI: 0.58 to 1.06; I^2 = N/A	N/A	1 RCT[28-37]

Abbreviations: APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable/not available; PR = progesterone receptor; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.18. Subgroup analyses. KQ 1: Resection margins

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI IORT vs. WBI	Resection margins	Negative or close	IBR	>10 years	RR: 4.56; 95% CI: 2.64 to 7.88; I^2 = N/A	APBI IORT: 10.71% (69/644) vs. WBI: 2.35% (15/638)	1 RCT[7, 8]
	Resection margins	Positive	IBR	>10 years	RR: 3.00; 95% CI: 0.26 to 34.57; I^2 = N/A	APBI IORT: 33.33% (1/3) vs. WBI: 11.11% (1/9)	1 RCT[7, 8]
	Resection margins	Negative or close	IBR	>10 years	HR: 4.78; 95% CI: 2.73 to 8.35; I^2 = N/A	APBI IORT: 10.71% (69/644) vs. WBI: 2.35% (15/638)	1 RCT[7, 8]
	Resection margins	Positive	IBR	>10 years	HR: 2.45; 95% CI: 0.15 to 39.72; I^2 = N/A	APBI IORT: 33.33% (1/3) vs. WBI: 11.11% (1/9)	1 RCT[7, 8]

Abbreviations: APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.19. Subgroup analyses. KQ 1: Tumor grade

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI 3DCRT vs. WBI	Tumor grade	Grade 1-2	IBR	10 years	HR: 1.10; 95% CI: 0.60 to 2.01; I^2 = N/A	N/A	1 RCT[22-24]
	Tumor grade	Grade 3	IBR	10 years	HR: 1.06; 95% CI: 0.44 to 2.55; I^2 = N/A	N/A	1 RCT[22-24]
APBI IMRT vs. WBI	Tumor grade	Grade 1	IBR	5 years	RR: 4.16; 95% CI: 0.20 to 85.69; I^2 = N/A	APBI IMRT: 1.61% (2/124) vs. WBI: 0% (0/103)	1 RCT[9-13]
	Tumor grade	Grade 2	IBR	5 years	RR: 0.23; 95% CI: 0.01 to 4.64; I^2 = N/A	APBI IMRT: 0% (0/110) vs. WBI: 1.61% (2/124)	1 RCT[9-13]
	Tumor grade	Grade 3	IBR	5 years	RR: 1.27; 95% CI: 0.08 to 19.34; I^2 = N/A	APBI IMRT: 3.85% (1/26) vs. WBI: 3.03% (1/33)	1 RCT[9-13]
APBI IORT vs. WBI	Tumor grade	Grade 1	IBR	>10 years	RR: 3.81; 95% CI: 1.11 to 13.02; I^2 = N/A	APBI IORT: 7.14% (14/196) vs. WBI: 1.88% (3/160)	1 RCT[7, 8]
	Tumor grade	Grade 2	IBR	>10 years	RR: 4.44; 95% CI: 2.08 to 9.45; I^2 = N/A	APBI IORT: 10.82% (33/305) vs. WBI: 2.44% (8/328)	1 RCT[7, 8]
	Tumor grade	Grade 3	IBR	>10 years	RR: 4.72; 95% CI: 1.83 to 12.16; I^2 = N/A	APBI IORT: 16.28% (21/129) vs. WBI: 3.45% (5/145)	1 RCT[7, 8]
	Tumor grade	Grade 1	IBR	>10 years	HR: 3.95; 95% CI: 1.13 to 13.74; I^2 = N/A	APBI IORT: 7.14% (14/196) vs. WBI: 1.88% (3/160)	1 RCT[7, 8]
	Tumor grade	Grade 2	IBR	>10 years	HR: 4.73; 95% CI: 2.18 to 10.24; I^2 = N/A	APBI IORT: 10.82% (33/305) vs. WBI: 2.44% (8/328)	1 RCT[7, 8]
	Tumor grade	Grade 3	IBR	>10 years	HR: 4.89; 95% CI: 1.84 to 12.96; I^2 = N/A	APBI IORT: 16.28% (21/129) vs. WBI: 3.45% (5/145)	1 RCT[7, 8]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
IORT during lumpectomy vs. WBI	Tumor grade	Grade 1-2	IBR	5 years	RR: 2.43; 95% CI: 1.01 to 5.83; I^2 = N/A	IORT during lumpectomy: 1.86% (17/914) vs. WBI: 0.77% (7/914)	1 RCT[28-37]
	Tumor grade	Grade 3	IBR	5 years	RR: 1.68; 95% CI: 0.50 to 5.66; I^2 = N/A	IORT during lumpectomy: 3.10% (7/226) vs. WBI: 1.84% (4/217)	1 RCT[28-37]
	Tumor grade	Grade 1-2	Overall survival	5 years	RR: 1.02; 95% CI: 1.00 to 1.03; I^2 = N/A	IORT during lumpectomy: 97.26% (889/914) vs. WBI: 95.73% (875/914)	1 RCT[28-37]
	Tumor grade	Grade 3	Overall survival	5 years	RR: 1.00; 95% CI: 0.95 to 1.06; I^2 = N/A	IORT during lumpectomy: 92.48% (209/226) vs. WBI: 92.17% (200/217)	1 RCT[28-37]
	Tumor grade	Grade 1-2	Overall survival	>10 years	HR: 0.72; 95% CI: 0.53 to 0.98; I^2 = N/A	N/A	1 RCT[28-37]
	Tumor grade	Grade 3	Overall survival	>10 years	HR: 1.09; 95% CI: 0.69 to 1.72; I^2 = N/A	N/A	1 RCT[28-37]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.20. Subgroup analyses. KQ 1: Tumor risk

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
IORT during lumpectomy vs. WBI	Tumor risk	Low risk (tumor not >2 cm, or grade 3 or ER-negative, irrespective of age or lymph node status	IBR	>10 years	HR: 0.95; 95% CI: 0.69 to 1.30; I^2 = N/A	N/A	1 RCT[28-37]
	Tumor risk	High risk (tumor >2 cm, or grade 3 or ER-negative, irrespective of age or lymph node status)	IBR	>10 years	HR: 0.81; 95% CI: 0.59 to 1.10; I^2 = N/A	N/A	1 RCT[28-37]

Abbreviations: CI = confidence interval; cm = centimeter; ER = estrogen receptor; HR = hazard ratio; IBR = ipsilateral breast recurrence; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; WBI = whole breast irradiation

Table J.21. Subgroup analyses. KQ 1: Tumor size

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI 3DCRT vs. WBI	Tumor size	<1.5 cm	IBR	10 years	HR: 1.02; 95% CI: 0.59 to 1.75; I^2 = N/A	N/A	1 RCT[22-24]
	Tumor size	≥1.5 cm	IBR	10 years	HR: 2.01; 95% CI: 1.03 to 3.93; I^2 = N/A	N/A	1 RCT[22-24]
APBI IORT vs. WBI	Tumor size	≤1.0 cm	IBR	>10 years	RR: 3.66; 95% CI: 1.24 to 10.82; I^2 = N/A	APBI IORT: 7.54% (15/199) vs. WBI: 2.06% (4/194)	1 RCT[7, 8]
	Tumor size	>1.0-1.5 cm	IBR	>10 years	RR: 5.42; 95% CI: 2.13 to 13.79; I^2 = N/A	APBI IORT: 11.52% (28/243) vs. WBI: 2.13% (5/235)	1 RCT[7, 8]
	Tumor size	>1.5-2.0 cm	IBR	>10 years	RR: 4.15; 95% CI: 1.21 to 14.19; I^2 = N/A	APBI IORT: 10.38% (13/120) vs. WBI: 2.61% (3/115)	1 RCT[7, 8]
	Tumor size	>2.0 cm	IBR	>10 years	RR: 4.34; 95% CI: 1.49 to 12.7; I^2 = N/A	APBI IORT: 16.87% (14/83) vs. WBI: 3.88% (4/103)	1 RCT[7, 8]
	Tumor size	≤1.0 cm	IBR	>10 years	HR: 4.01; 95% CI: 1.33 to 12.1; I^2 = N/A	APBI IORT: 7.54% (15/199) vs. WBI: 2.06% (4/194)	1 RCT[7, 8]
	Tumor size	>1.0-1.5 cm	IBR	>10 years	HR: 5.73; 95% CI: 2.21 to 14.83; I^2 = N/A	APBI IORT: 11.52% (28/243) vs. WBI: 2.13% (5/235)	1 RCT[7, 8]
	Tumor size	>1.5-2.0 cm	IBR	>10 years	HR: 3.75; 95% CI: 1.06 to 13.24; I^2 = N/A	APBI IORT: 10.38% (13/120) vs. WBI: 2.61% (3/115)	1 RCT[7, 8]
	Tumor size	>2.0 cm	IBR	>10 years	HR: 4.8; 95% CI: 1.58 to 14.58; I^2 = N/A	APBI IORT: 16.87% (14/83) vs. WBI: 3.88% (4/103)	1 RCT[7, 8]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT vs. WBI	Tumor size	≤1 cm	IBR	10 years	RR: 0.54; 95% CI: 0.26 to 1.11; I^2 = N/A*	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 1.89% (11/581) vs. WBI:3.53% (20/567)	1 RCT[19]
	Tumor size	1.1-2.0 cm	IBR	10 years	RR: 2.79; 95% CI: 1.32 to 5.91; I^2 = N/A*	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 4.06% (26/641) vs. WBI: 1.45% (9/620)	1 RCT[19]
	Tumor size	≥2 cm	IBR	10 years	RR: 1.30; 95% CI: 0.52 to 3.21; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 5.41% (10/185) vs. WBI: 4.17% (8/192)	1 RCT[19]
	Tumor size	≤1 cm	IBR	10 years	HR: 0.58; 95% CI: 0.27 to 1.22; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 1.89% (11/581) vs. WBI:3.53% (20/567)	1 RCT[19]
	Tumor size	1.1-2.0 cm	IBR	10 years	HR: 2.66; 95% CI: 1.24 to 5.68; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 4.06% (26/641) vs. WBI: 1.45% (9/620)	1 RCT[19]
	Tumor size	≥2 cm	IBR	10 years	HR: 1.34; 95% CI: 0.52 to 3.46; I^2 = N/A	APBI single-entry catheter brachytherapy, multi-catheter interstitial brachytherapy, or 3DCRT: 5.41% (10/185) vs. WBI: 4.17% (8/192)	1 RCT[19]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
IORT during lumpectomy vs. WBI	Tumor size	≤1 cm	IBR	5 years	RR: 5.01; 95% CI: 1.11 to 22.72; I^2 = N/A	IORT during lumpectomy: 2.71% (10/369) vs. WBI: 0.54% (2/370)	1 RCT[28-37]
	Tumor size	1.1-2.0 cm	IBR	5 years	RR: 2.15; 95% CI: 0.75 to 6.14; I^2 = N/A	IORT during lumpectomy: 1.93% (11/571) vs. WBI: 0.90% (5/557)	1 RCT[28-37]
	Tumor size	>2 cm	IBR	5 years	RR: 0.72; 95% CI: 0.12 to 4.26; I^2 = N/A	IORT during lumpectomy: 1.14% (2/176) vs. WBI: 1.58% (3/190)	1 RCT[28-37]
	Tumor size	≤1 cm	Overall survival	5 years	RR: 1.01; 95% CI: 0.98 to 1.03; I^2 = N/A	IORT during lumpectomy: 97.83% (361/369) vs. WBI: 97.30% (360/370)	1 RCT[28-37]
	Tumor size	1.1-2.0 cm	Overall survival	5 years	RR: 1.02; 95% CI: 0.99 to 1.04; I^2 = N/A	IORT during lumpectomy: 97.20% (555/571) vs. WBI: 95.51% (532/557)	1 RCT[28-37]
	Tumor size	>2 cm	Overall survival	5 years	RR: 1.00; 95% CI: 0.94 to 1.08; I^2 = N/A	IORT during lumpectomy: 89.77% (158/176) vs. WBI: 89.47% (170/190)	1 RCT[28-37]
	Tumor size	≤1 cm	Overall survival	>10 years	HR: 0.84; 95% CI: 0.48 to 1.49; I^2 = N/A	N/A	1 RCT[28-37]
	Tumor size	1.1-2.0 cm	Overall survival	>10 years	HR: 0.73; 95% CI: 0.50 to 1.05; I^2 = N/A	N/A	1 RCT[28-37]
	Tumor size	>2 cm	Overall survival	>10 years	HR: 1.00; 95% CI: 0.64 to 1.57; I^2 = N/A	N/A	1 RCT[28-37]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; APBI = accelerated partial breast irradiation; CI = confidence interval; cm = centimeter; HR = hazard ratio; IBR = ipsilateral breast recurrence; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

*: Statistically significant difference between tumor size of ≤1 cm and tumor size of 1.1-2.0 cm (p=0.002)

Table J.22. Subgroup analyses. KQ 1: Treatment schedule

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
PBI vs. WBI	Treatment schedule	Accelerated PBI	Cancer-free survival	5 years	RR: 1.00; 95% CI: 0.96 to 1.04; I^2 =0%	PBI: 91.47% (1695/1853) vs. WBI: 91.92% (1717/1868)	3 RCTs[1, 14-17, 22-24]
	Treatment schedule	Nonaccelerated PBI	Cancer-free survival	5 years	RR: 1.00; 95% CI: 0.98 to 1.03; I^2 = N/A	PBI: 95.10% (641/674) vs. WBI: 95.07% (636/669)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	Contralateral breast cancer recurrence	5 years	RR: 1.01; 95% CI: 0.19 to 5.25; I^2 = 36.11%	PBI: 1.33% (15/1125) vs. WBI: 1.30% (15/1153)	4 RCTs[1, 9-18, 25, 26]
	Treatment schedule	Nonaccelerated PBI	Contralateral breast cancer recurrence	5 years	RR: 1.08; 95% CI: 0.49 to 2.34; I^2 = N/A	PBI: 1.93% (13/674) vs. WBI: 1.79% (12/669)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	Distant breast cancer recurrence	5 years	RR: 0.92; 95% CI: 0.38 to 2.24; I^2 = 0%	PBI: 1.45% (17/1176) vs. WBI: 1.58% (19/1204)	5 RCTs[1, 9-18, 25, 26]
	Treatment schedule	Nonaccelerated PBI	Distant breast cancer recurrence	5 years	RR: 0.92; 95% CI: 0.42 to 1.99; I^2 = N/A	PBI: 1.78% (12/674) vs. WBI: 1.94% (13/669)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	Elsewhere IBR	5 years	RR: 2.04; 95% CI: 0.09 to 45.84; I^2 = 0%	PBI: 1.37% (6/439) vs. WBI: 0.45% (2/441)	3 RCTs[1, 9-13, 25, 26]
	Treatment schedule	Nonaccelerated PBI	Elsewhere IBR	5 years	RR: 0.33; 95% CI: 0.01 to 8.11; I^2 = N/A	PBI: 0% (0/674) vs. WBI: 0.15% (1/669)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	IBR	5 years	RR: 1.53; 95% CI: 0.88 to 2.63; I^2 = 0%	PBI: 2.12% (49/2316) vs. WBI: 1.37% (32/2339)	7 RCTs[1, 9-18, 22-27]
	Treatment schedule	Nonaccelerated PBI	IBR	5 years	RR: 0.66; 95% CI: 0.24 to 1.85; I^2 = N/A	PBI: 0.89% (6/)674 vs. WBI: 1.35% (9/669)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	Overall survival	5 years	RR: 1; 95% CI: 0.99 to 1.01; I^2 = 0%	PBI: 96.47% (2185/2265) vs. WBI: 96.42% (2206/2288)	6 RCTs[1, 9-18, 22-24, 27]
	Treatment schedule	Nonaccelerated PBI	Overall survival	5 years	RR: 0.99; 95% CI: 0.96 to 1.02; I^2 = N/A	PBI: 93.77% (632/674) vs. WBI: 94.77% (634/669)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	Total AE	Late AE	IRR: 0.86; 95% CI: 0.40 to 1.88; I^2 = 96.99%	PBI: 68.92% (3045/4418) vs. WBI: 62.02% (2757/4445)	8 RCTs[1, 9-19, 22-26, 38]
	Treatment schedule	Nonaccelerated PBI	Total AE	Late AE	IRR: 0.79; 95% CI: 0.70 to 0.89; I^2 = N/A	PBI: 68.91% (461/669) vs. WBI: 87.54% (590/674)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	Tumor bed IBR	5 years	RR: 1.01; 95% CI: 0.08 to 13.24; I^2 = 0%	PBI: 1.14% (5/439) vs. WBI: 1.13% (5/441)	3 RCTs[1, 9-13, 25, 26]
	Treatment schedule	Nonaccelerated PBI	Tumor bed IBR	5 years	RR: 0.44; 95% CI: 0.14 to 1.43; I^2 = N/A	PBI: 0.59% (4/674) vs. WBI: 1.35% (9/669)	1 RCT[20, 21]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
3DCRT vs. WBI	Treatment schedule	Accelerated PBI	Cancer-free survival	5 years	RR: 0.99; 95% CI: 0.96 to 1.02; I^2 = N/A	3DCRT: 89.35% (956/1070) vs. WBI: 90.52% (964/1065)	1 RCT[22-24]
	Treatment schedule	Nonaccelerated PBI	Cancer-free survival	5 years	RR: 1.00; 95% CI: 0.98 to 1.03; I^2 = N/A	3DCRT: 95.10% (641/674) vs. WBI: 95.07% (636/669)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	Distant breast cancer recurrence	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A	3DCRT: 0% (0/51) vs. WBI: 0% (0/51)	1 RCT[25, 26]
	Treatment schedule	Nonaccelerated PBI	Distant breast cancer recurrence	5 years	RR: 0.92; 95% CI: 0.42 to 1.99; I^2 = N/A	3DCRT: 1.78% (12/674) vs. WBI: 0.45% (13/669)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	Elsewhere IBR	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A	3DCRT: 0% (0/51) vs. WBI: 0% (0/51)	1 RCT[25, 26]
	Treatment schedule	Nonaccelerated PBI	Elsewhere IBR	5 years	RR: 0.33; 95% CI: 0.01 to 8.11; I^2 = N/A	3DCRT: 0% (0/674) vs. WBI: 0.001% (1/669)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	IBR	5 years	RR: 1.36; 95% CI: 0.38 to 4.93; I^2 = 0%	3DCRT: 2.10%% (25/1191) vs. WBI: 1.51% (18/1186)	3 RCTs[22-27]
	Treatment schedule	Nonaccelerated PBI	IBR	5 years	RR: 0.66; 95% CI: 0.24 to 1.85; I^2 = N/A	3DCRT: 0.89% (6/674) vs. WBI: 1.35% (9/669)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	Total AE	Late AE	IRR: 0.70; 95% CI: 0.01 to 70.47; I^2 =79.63%	3DCRT: 68.97% (80/116) vs. WBI: 116.10% (137/118)	2 RCTs[25, 26, 38]
	Treatment schedule	Nonaccelerated PBI	Total AE	Late AE	IRR: 0.79; 95% CI: 0.70 to 0.89; I^2 = N/A	3DCRT: 68.91% (461/669) vs. WBI: 87.54% (590/674)	1 RCT[20, 21]
	Treatment schedule	Accelerated PBI	Tumor bed IBR	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A	3DCRT: 0% (0/51) vs. WBI: 0% (0/51)	1 RCT,[25, 26]
	Treatment schedule	Nonaccelerated PBI	Tumor bed IBR	5 years	RR: 0.44; 95% CI: 0.14 to 1.43; I^2 = N/A	3DCRT: 0.59% (4/674) vs. WBI: 1.35% (9/669)	1 RCT[20, 21]

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; AE = adverse event; CI = confidence interval; IBR = ipsilateral breast recurrence; IRR = incidence rate ration; KQ = Key Question; N/A = not applicable; PBI = partial breast irradiation; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Table J.23. Subgroup analyses. KQ 1: Fractionation regimen

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
PBI compared with WBI	Fractionation	Twice/day	Cancer-free survival	5 years	RR: 0.99; 95% CI: 0.96 to 1.02; I^2 = N/A	PBI: 89.35% (956/1070) vs. WBI: 90.52% (964/1065)	1 RCT[22-24]
	Fractionation	Once/day	Cancer-free survival	5 years	RR: 1.00; 95% CI: 0.98 to 1.03; I^2 = N/A	PBI: 95.10% (641/674) vs. WBI: 95.07% (636/)669	1 RCT[20, 21]
	Fractionation	Once/day	Contralateral breast cancer recurrence	5 years	RR:1.08; 95% CI: 0.49 to 2.34; I^2 = N/A	PBI: 1.93% (13/674) vs. WBI: 1.79% (12/669)	1 RCT[20]
	Fractionation	Every 2 days	Contralateral breast cancer recurrence	5 years	RR: 0.34; 95% CI: .00 to ∞; I^2 = 0.00%	PBI: 0.58% (2/342) vs. WBI: 2% (7/350)	2 RCTs[9-13, 18]
	Fractionation	Every 2 days	Contralateral breast cancer recurrence	10 years	RR: 0.25; 95% CI: 0.05 to 1.17; I^2 = N/A	PBI: 0.77% (2/260) vs. WBI: 3.08% (8/260)	1 RCT[9-13]
	Fractionation	Twice/day	Contralateral breast cancer recurrence	10 years	RR: 0.76; 95% CI: 0.47 to 1.22; I^2 = N/A	PBI: 2.71% (29/1070) vs. WBI: 3.57% (38/1065)	1 RCT,[22-24]
	Fractionation	Twice/day	Cosmesis reported by patient (poor or fair)	10 years	RR: 2.32; 95% CI: 1.84 to 2.91; I^2 = N/A*	PBI: 20% (214/1070) vs. WBI: 8.64% (92/1065)	1 RCT[22-24]
	Fractionation	Every 2 days	Cosmesis reported by patient (poor or fair)	10 years	RR: 0.05; 95% CI: 0.01 to 0.22; I^2 = N/A*	PBI: 0.77% (2/260) vs. WBI: 14.62% (38/)260	1 RCT[9-13]
	Fractionation	Twice/day	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 1.01; 95% CI: 0.03 to 31.89; I^2 = 90.77%	PBI: 25.04% (297/1186) vs. WBI: 13.36% (158/1183)	3 RCTs[22-26, 38]
	Fractionation	Every 2 days	Cosmesis reported by healthcare provider (poor or fair)	5 years	RR: 0.43; 95% CI: 0.00 to ∞; I^2 = 0.00%	PBI: 0.58% (2/342) vs. WBI: 1.71% (6/350)	2 RCTs[9-13, 18]
	Fractionation	Twice/day	Cosmesis reported by healthcare provider (poor or fair)	10 years	RR: 2.14; 95% CI: 1.74 to 2.61; I^2 =N/A[$]	PBI: 4.77% (251/1070) vs. WBI: 10.99% (117/1065)	1 RCT[22-24]
	Fractionation	Every 2 days	Cosmesis reported by healthcare provider (poor or fair)	10 years	RR: 0.09; 95% CI: 0.01 to 1.64; I^2 = N/A[$]	PBI: 0% (0/260) vs. WBI: 1.92% (5/)260	1 RCT[9-13]
	Fractionation	Twice/day	Distant breast cancer recurrence	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A	PBI: 0% (0/51) vs. WBI: 0% (0/51)	1 RCT[25, 26]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
PBI compared with WBI (continued)	Fractionation	Once/day	Distant breast cancer recurrence	5 years	RR: 0.92; 95% CI: 0.42 to 1.99; I^2 = N/A	PBI: 1.78% (12/674) vs. WBI: 1.94% (13/669)	1 RCT[20]
	Fractionation	Every 2 days	Distant breast cancer recurrence	5 years	RR: 0.70; 95% CI: 0 to ∞; I^2 = 0.00%	PBI: 1.17% (4/342) vs. WBI: 1.71% (6/350)	2 RCTs[9-13, 18]
	Fractionation	Twice/day	Distant breast cancer recurrence	10 years	RR: 1.11; 95% CI: 0.59 to 2.08; I^2 = N/A	PBI: 1.87% (20/1070) vs. WBI: 1.69% (18/1065)	1 RCT[22-24]
	Fractionation	Once/day	Distant breast cancer recurrence	10 years	RR: 0.85; 95% CI: 0.50 to 1.43; I^2 = N/A	PBI: 22.62% (19/84) vs. WBI: 26.67% (24/90)	1 RCT[6]
	Fractionation	Every 2 days	Distant breast cancer recurrence	10 years	RR: 0.88; 95% CI: 0.32 to 2.38; I^2 = N/A	PBI: 2.69% (7/260) vs. WBI: 3.08% (7/260)	1 RCT[9-13]
	Fractionation	Twice/day	Elsewhere IBR	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A	PBI: 0% (0/51) vs. WBI: 0% (0/51)	1 RCT[25, 26]
	Fractionation	Once/day	Elsewhere IBR	5 years	RR: 0.33; 95% CI: 0.01 to 8.11; I^2 = N/A	PBI: 0% (0/674) vs. WBI: 0.15% (1/669)	1 RCT [20]
	Fractionation	Every 2 days	Elsewhere IBR	5 years	RR: 7.00; 95% CI: 0.36 to 134.84; I^2 = N/A	PBI: 1.15% (3/260) vs. WBI: 0% (0/260)	1 RCT[9-13]
	Fractionation	Twice/day	Elsewhere IBR	10 years	RR: 2.49; 95% CI: 1.10 to 5.62; I^2 = N/A	PBI: 1.87% (20/1070) vs. WBI: 0.75% (8/1065)	1 RCT[22-24]
	Fractionation	Every 2 days	Elsewhere IBR	10 years	RR: 2.00; 95% CI: 0.37 to 10.82; I^2 = N/A	PBI: 1.54% (4/260) vs. WBI: 0.77% (2/260)	1 RCT[9-13]
	Fractionation	Twice/day	IBR	5 years	RR: 1.37; 95% CI: 0.03 to 64.08; I^2 = 0.0%	PBI: 2.23% (25/1121) vs. WBI: 1.61% (18/1116)	2 RCTs[22-26]
	Fractionation	Once/day	IBR	5 years	RR: 0.66; 95% CI: 0.24 to 1.85; I^2 = N/A	PBI: 0.89% (6/674) vs. WBI: 1.35% (9/669)	1 RCT[20]
	Fractionation	Every 2 days	IBR	5 years	RR: 1.86; 95% CI: 0.00 to ∞; I^2 = 0.00%	PBI: 2.63% (9/342) vs. WBI: 1.43% (5/350)	2 RCTs[9-13, 18]
	Fractionation	Twice/day	IBR	10 years	RR: 1.28; 95% CI: 0.24 to 6.83; I^2 = 0.0%	PBI: 4% (127/3177) vs. WBI: 3.12% (99/3174)	2 RCTs[19, 22-24]
	Fractionation	Once/day	IBR	10 years	RR: 2.68; 95% CI: 0.87 to 8.22; I^2 = N/A	PBI: 11.90% (10/84) vs. WBI: 4.44% (4/90)	1 RCT[6]
	Fractionation	Every 2 days	IBR	10 years	RR: 1.50; 95% CI: 0.54 to 4.15; I^2 = N/A	PBI: 3.46% (9/260) vs. WBI: 2.31% (6/260)	1 RCT[9-13]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
PBI compared with WBI (continued)	Fractionation	Twice/day	Overall survival	5 years	RR: 0.99; 95% CI: 0.98 to 1.01; I^2 = N/A	PBI: 96.17% (1029/1070) vs. WBI: 97% (1033/1065)	1 RCT[22-24]
	Fractionation	Once/day	Overall survival	5 years	RR: 0.99; 95% CI: 0.96 to 1.02; I^2 = N/A	PBI: 93.77% (632/674) vs. WBI: 94.77% (634/669)	1 RCT[20]
	Fractionation	Every 2 days	Overall survival	5 years	RR: 1.00; 95% CI: 0.90 to 1.13; I^2 = 0.00%	PBI: 98.54% (337/342) vs. WBI: 97.71% (342/350)	2 RCT[9-13, 18]
	Fractionation	Twice/day	Overall survival	10 years	RR: 1.00; 95% CI: 0.83 to 1.22; I^2 = 73.8%	PBI: 90.97% (2890/3177) vs. WBI: 90.20% (2863/3174)	2 RCTs[19, 22-24]
	Fractionation	Once/day	Overall survival	10 years	RR: 0.96; 95% CI: 0.79 to 1.15; I^2 = N/A	PBI: 70.24% (59/84) vs. WBI: 73.33% (66/90)	1 RCT[6]
	Fractionation	Every 2 days	Overall survival	10 years	RR: 1.01; 95% CI: 0.96 to 1.06; I^2 = N/A	PBI: 93.08% (242/260) vs. WBI: 92.30% (240/260)	1 RCT[9-13]
	Fractionation	Twice/day	Total AE	Acute	IRR: 0.69; 95% CI: 0.34 to 1.40; I^2 = N/A[#]	PBI: 37.52% (445/1186) vs. WBI: 62.55% (740/1183)	3 RCTs[22-26, 38]
	Fractionation	Every 2 days	Total AE	Acute	IRR: 0.28; 95% CI: 0.21 to 0.38; I^2 = 0.00%[#]	PBI: 18.42% (63/342) vs. WBI: 65.43% (229/350)	2 RCTs[9-13, 18]
	Fractionation	Twice/day	Total AE	Late	IRR: 1.21; 95% CI: 0.30 to 4.80; I^2 = 98.3%	PBI: 76.25% (2511/3293) vs. WBI: 67.42% (2220/3292)	4 RCTs[19, 22-26, 38]
	Fractionation	Once/day	Total AE	Late	IRR: 0.79; 95% CI: 0.70 to 0.89; I^2 = N/A	PBI: 68.91% (461/669) vs. WBI: 87.54% (590/674)	1 RCT[20]
	Fractionation	Every 2 days	Total AE	Late	IRR: 0.26; 95% CI: 0.00 to 223.07; I^2 = 83.17%	PBI: 7.89% (27/342) vs. WBI: 32.86% (115/350)	2 RCTs[9-13, 18]
	Fractionation	Twice/day	Tumor bed IBR	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A	PBI: 0% (0/51) vs. WBI: 0% (0/51)	1 RCT[25, 26]
	Fractionation	Once/day	Tumor bed IBR	5 years	RR: 0.44; 95% CI: 0.14 to 1.43; I^2 = N/A	PBI: 0.59% (4/674) vs. WBI: 1.35% (9/669)	1 RCT[20]
	Fractionation	Every 2 days	Tumor bed IBR	5 years	RR: 1.00; 95% CI: 0.20 to 4.91; I^2 =N/A	PBI: 1.15% (3/260) vs. WBI: 1.15% (3/260)	1 RCT[9-13]
	Fractionation	Twice/day	Tumor bed IBR	10 years	RR: 0.85; 95% CI: 0.45 to 1.61; I^2 = N/A	PBI: 1,59% (17/1070) vs. WBI: 1.88% (20/1065)	1 RCT[22-24]
	Fractionation	Every 2 days	Tumor bed IBR	10 years	RR: 1.25; 95% CI: 0.34 to 4.60; I^2 = N/A	PBI: 1.92% (5/260) vs. WBI: 1,54% (4/260)	1 RCT[9-13]

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
3DCRT compared with WBI	Fractionation	Twice/day	Cancer-free survival	5 years	RR: 0.99; 95% CI: 0.96 to 1.02; I^2 = N/A	PBI: 89.35% (956/1070) vs. WBI: 90.52% (964/1065)	1 RCT[22-24]
	Fractionation	Once/day	Cancer-free survival	5 years	RR: 1.00; 95% CI: 0.98 to 1.03; I^2 = N/A	3DCRT: 95.10% (641/674) vs. WBI: 95.07% (636/669)	1 RCT[20, 21]
	Fractionation	Twice/day	Distant breast cancer recurrence	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A	3DCRT: 0% (0/51) vs. WBI: 0% (0/51)	1 RCT[25, 26]
	Fractionation	Once/day	Distant breast cancer recurrence	5 years	RR: 0.92; 95% CI: 0.42 to 1.99; I^2 = N/A	3DCRT: 1.78% (12/674) vs. WBI: 1.94% (13/669)	1 RCT[20, 21]
	Fractionation	Twice/day	Elsewhere IBR	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A	3DCRT: 0% (0/51) vs. WBI: 0% (0/51)	1 RCT[25, 26]
	Fractionation	Once/day	Elsewhere IBR	5 years	RR: 0.33; 95% CI: 0.01 to 8.11; I^2 = N/A	3DCRT: 0% (0/674) vs. WBI: 0.15% (1/669)	1 RCT[20, 21]
	Fractionation	Twice/day	IBR	5 years	RR: 1.37; 95% CI: 0.03 to 64.08; I^2 = 0.0%	3DCRT: 2.23% (25/1121) vs. WBI: 1.61% (18/1116)	2 RCTs[22-26]
	Fractionation	Once/day	IBR	5 years	RR: 0.66; 95% CI: 0.24 to 1.85; I^2 = N/A	3DCRT: 0.89% (6/674) vs. WBI: 1.35% (9/669)	1 RCT[20, 21]
	Fractionation	Twice/day	Overall survival	5 years	RR: 0.99; 95% CI: 0.98 to 1.01; I^2 = N/A	3DCRT: 96.17% (1029/1070) vs. WBI: 97% (1033/)1065	1 RCT[22-24]
	Fractionation	Once/day	Overall survival	5 years	RR: 0.99; 95% CI: 0.96 to 1.02; I^2 = N/A	3DCRT: 93.77% (632/674) vs. WBI: 94.77% (634/669)	1 RCT[20, 21]
	Fractionation	Twice/day	Total AE	Late	IRR: 1.28; 95% CI: 0.05 to 32.02; I^2 = 98.30%	3DCRT: 45.03% (534/1186) vs. WBI: 21.30% (252/1183)	3 RCTs [22-26, 38]
	Fractionation	Once/day	Total AE	Late	IRR: 0.79; 95% CI: 0.70 to 0.89; I^2 = N/A	3DCRT: 68.91% (461/669) vs. WBI: 87.54% (590/674)	1 RCT[20, 21]
	Fractionation	Twice/day	Tumor bed IBR	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A	3DCRT: 0% (0/51) vs. WBI: 0% (0/51)	1 RCT[25, 26]
	Fractionation	Once/day	Tumor bed IBR	5 years	RR: 0.44; 95% CI: 0.14 to 1.43; I^2 = N/A	3DCRT: 0.59% (4/674) vs. WBI: 1.35% (9/669)	1 RCT[20, 21]

Abbreviations: ∞ = infinity; 3DCRT: 3-dimensional conformal external beam radiation therapy; AE: adverse event; CI: confidence interval; IBR: ipsilateral breast recurrence; IRR = incidence rate ration; KQ = Key Question; N/A: not applicable; PBI: partial breast irradiation; RCT = randomized clinical trial; RR: relative risk; WBI: whole breast irradiation

*: Statistically significant difference between fractionation of twice/day and once/day ($p<0.001$)
$: Statistically significant difference between fractionation of twice/day and once/day ($p=0.02$)
#: Statistically significant difference between fractionation of twice/day and once/day ($p=0.03$) and between twice/day and once every 2 days ($p=0.02$)

Table J.24. Subgroup analyses. KQ 1: Treatment schedule – delayed versus immediate IORT

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings	Percentage (Events/Patients)	Study Design
IORT vs. WBI	Treatment schedule	Delayed IORT as a second procedure	IBR	5 years	RR: 3.77; 95% CI: 1.55 to 9.20; I^2 = N/A	N/A	1 RCT[30]
	Treatment schedule	Immediate IORT during lumpectomy	IBR	5 years	RR: 2.22; 95% CI: 1.09 to 4.50; I^2 = N/A	N/A	1 RCT[31]
	Treatment schedule	Delayed IORT as a second procedure	Mastectomy-free survival	>10 years	RR: 0.98; 95% CI: 0.93 to 1.02; I^2 = N/A	N/A	1 RCT[30]
	Treatment schedule	Immediate IORT during lumpectomy	Mastectomy-free survival	>10 years	RR: 1.00; 95% CI: 0.97 to 1.04; I^2 = N/A	N/A	1 RCT[31]
	Treatment schedule	Delayed IORT as a second procedure	Overall survival	5 years	RR: 0.99; 95% CI: 0.97 to 1.01; I^2 = N/A	N/A	1 RCT[30]
	Treatment schedule	Immediate IORT during lumpectomy	Overall survival	5 years	RR: 1.01; 95% CI: 0.99 to 1.03; I^2 = N/A	N/A	1 RCT[31]
	Treatment schedule	Delayed IORT as a second procedure	Overall survival	>10 years	RR: 0.99; 95% CI: 0.95 to 1.03; I^2 = N/A	N/A	1 RCT[30]
	Treatment schedule	Immediate IORT during lumpectomy	Overall survival	>10 years	RR: 1.02; 95% CI: 0.99 to 1.05; I^2 = N/A	N/A	1 RCT[31]

Abbreviations: CI = confidence interval; IBR = ipsilateral breast recurrence; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable/not available; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

Appendix K. Comparison by Risk of Bias

Table K.1. Comparison by risk of bias

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings
PBI vs. WBI	ROB	High	Cancer-free survival	5 years	RR: 1.02; 95% CI: 0.94 to 1.10; I^2 = N/A
	ROB	Moderate	Cancer-free survival	5 years	RR: 1; 95% CI: 0.98 to 1.03; I^2 = N/A
	ROB	Low	Cancer-free survival	5 years	RR: 0.99; 95% CI: 0.88 to 1.12; I^2 = 0%
	ROB	High	Cancer-free survival	10 years	RR: 0.97; 95% CI: 0.87 to 1.08; I^2 = N/A
	ROB	Low	Cancer-free survival	10 years	RR: 0.97; 95% CI: 0.83 to 1.13; I^2 = 0%
	ROB	High	Contralateral breast cancer recurrence	5 years	RR: 2.47; 95% CI: 0.00 to ∞; I^2 = 0%
	ROB	Moderate	Contralateral breast cancer recurrence	5 years	RR: 1.03; 95% CI: 0.30 to 3.53; I^2 = N/A
	ROB	Low	Contralateral breast cancer recurrence	5 years	RR: 0.66; 95% CI: 0.00 to ∞; I^2 = 54.89%
	ROB	High	Contralateral breast cancer recurrence	10 years	RR: 1.16; 95% CI: 0.43 to 3.11; I^2 = N/A
	ROB	Low	Contralateral breast cancer recurrence	10 years	RR: 0.56; 95% CI: 0.00 to 304.33; I^2 = 45.25%
	ROB	High	Distant breast cancer recurrence	5 years	RR: 1.02; 95% CI: 0.14 to 7.31; I^2 = 0%
	ROB	Moderate	Distant breast cancer recurrence	5 years	RR: 1.03; 95% CI: 0.3 to 3.53; I^2 = N/A
	ROB	Low	Distant breast cancer recurrence	5 years	RR: 0.84; 95% CI: 0.01 to 60.74; I^2 = 0%
	ROB	High	Distant breast cancer recurrence	10 years	RR: 0.70; 95% CI: 0.31 to 1.59; I^2 = N/A
	ROB	Low	Distant breast cancer recurrence	10 years	RR: 1.03; 95% CI: 0.03 to 32.9; I^2 = 0%
	ROB	High	IBR	5 years	RR: 1.52; 95% CI: 0.18 to 13.13; I^2 = 0%
	ROB	Moderate	IBR	5 years	RR: 1.85; 95% CI: 0.62 to 5.49; I^2 = N/A
	ROB	Low	IBR	5 years	RR: 1.23; 95% CI: 0.42 to 3.60; I^2 = 1.19%
	ROB	High	IBR	10 years	RR: 1.18; 95% CI: 0.41 to 3.43; I^2 = N/A
	ROB	Low	IBR	10 years	RR: 1.29; 95% CI: 0.75 to 2.24; I^2 = 0%
	ROB	High	Overall survival	5 years	RR: 1.00; 95% CI: 0.87 to 1.15; I^2 = 0%
	ROB	Moderate	Overall survival	5 years	RR: 1.01; 95% CI: 0.98 to 1.03; I^2 = N/A
	ROB	Low	Overall survival	5 years	RR: 1.00; 95% CI: 0.97 to 1.02; I^2 = 0%
	ROB	High	Overall survival	10 years	RR: 1.05; 95% CI: 0.92 to 1.19; I^2 = N/A

Comparison	Subgroup	Subgroup Category	Outcome	Time Point	Findings
PBI vs. WBI (continued)	ROB	Low	Overall survival	10 years	RR: 1; 95% CI: 0.96 to 1.05; I^2 = 47.97%
	ROB	High	Total AE	Acute	IRR: 0.54; 95% CI: 0.08 to 3.64; I^2 = 85.73%
	ROB	Moderate	Total AE	Acute	IRR: 0.71; 95% CI: 0.64 to 0.80; I^2 = N/A
	ROB	Low	Total AE	Acute	IRR: 0.42; 95% CI: 0.01 to 24.41; I^2 = 92.88%
	ROB	High	Total AE	Late	IRR: 0.72; 95% CI: 0.32 to 1.62; I^2 = 83.86%
	ROB	Moderate	Total AE	Late	IRR: 1.01; 95% CI: 0.89 to 1.13; I^2 = N/A
	ROB	Low	Total AE	Late	IRR: 0.90; 95% CI: 0.12 to 6.92; I^2 = 98.64%
3DCRT vs. WBI	ROB	High	Distant breast cancer recurrence	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A
	ROB	Low	Distant breast cancer recurrence	5 years	RR: 0.92; 95% CI: 0.42 to 1.99; I^2 = N/A
	ROB	High	IBR	5 years	RR: 1.00; 95% CI: 0.02 to 49.45; I^2 = N/A
	ROB	Low	IBR	5 years	RR: 1.08; 95% CI: 0.01 to 89.18; I^2 = 32.11%
	ROB	High	Total AE	Late	IRR: 1.75; 95% CI: 0.00 to +∞; I^2 = 99.43%
	ROB	Low	Total AE	Late	IRR: 0.79; 95% CI: 0.70 to 0.89; I^2 = N/A
IMRT vs. WBI	ROB	High	Contralateral breast cancer recurrence	5 years	RR: 1.10; 95% CI: 0.02 to 54.63; I^2 = N/A
	ROB	Low	Contralateral breast cancer recurrence	5 years	RR: 0.29; 95% CI: 0.06 to 1.36; I^2 = N/A
	ROB	High	Distant breast cancer recurrence	5 years	RR: 1.10; 95% CI: 0.02 to 54.63; I^2 = N/A
	ROB	Low	Distant breast cancer recurrence	5 years	RR: 0.67; 95% CI: 0.19 to 2.33; I^2 = N/A
	ROB	High	IBR	5 years	RR: 1.65; 95% CI: 0.28 to 9.61; I^2 = N/A
	ROB	Low	IBR	5 years	RR: 2.00; 95% CI: 0.51 to 7.91; I^2 = N/A
	ROB	High	Overall survival	5 years	RR: 1.00; 95% CI: 0.98 to 1.02; I^2 = N/A
	ROB	Low	Overall survival	5 years	RR: 1.01; 95% CI: 0.98 to 1.04; I^2 = N/A
	ROB	High	Total AE	Acute	IRR: 0.22; 95% CI: 0.11 to 0.41; I^2 = N/A
	ROB	Low	Total AE	Acute	IRR: 0.30; 95% CI: 0.22 to 0.41; I^2 = 0%
	ROB	High	Total AE	Late	IRR: 0.44; 95% CI: 0.24 to 0.81; I^2 = N/A
	ROB	Low	Total AE	Late	IRR: 0.15; 95% CI: 0.08 to 0.28; I^2 = 100%
Multi-catheter interstitial brachytherapy vs. 3DCRT	ROB	High	Total AE	Late	IRR: 1.18; 95% CI: 0.79 to 1.77; I^2 = N/A
	ROB	Moderate	Total AE	Late	IRR: 1.01; 95% CI: 0.89 to 1.13; I^2 = 100%

Abbreviations: ∞ = infinity; 3DCRT = 3-dimensional conformal external beam radiation therapy; AE = adverse event; CI = confidence interval; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IRR = incidence rate ration; N/A = not applicable; PBI = partial breast irradiation; ROB = risk of bias; RR = relative risk; WBI = whole breast irradiation

Appendix L. Sensitivity Analysis

Table L.1. Meta-analysis with hazard ratio

Comparison	Outcome	Time	Findings	Study Design and Sample Size
PBI compared with WBI	IBR	5 years	HR: 0.77; 95% CI: 0.00 to 221.73; I^2 =0%	2 RCTs,[9, 20] 1,863 patients
	IBR	10 years	HR: 1.25; 95% CI: 0.72 to 2.18; I^2 =0.00	3 RCTs,[9, 19, 22] 6,871 patients
	Overall survival	5 years	HR: 1.83; 95% CI: 0.00 to ∞; I^2 =N/A	2 RCTs,[9, 20] 1,863 patients
	Overall survival	10 years	HR: 0.90; 95% CI: 0.62 to 1.29; I^2 =0%	3 RCTs,[9, 19, 22] 6,871 patients
	Overall survival	>10 years	HR: 0.98; 95% CI: 0.66 to 1.46; I^2 = N/A	1 RCT,[1] 258 patients
3DCRT compared with WBI	IBR	5 years	HR: 0.65; 95% CI: 0.23 to 1.84; I^2 =N/A	1 RCT,[20] 1,343 patients
	Overall survival	5 years	HR: 1.10; 95% CI: 0.70 to 1.72; I^2 =N/A	1 RCT,[20] 1,343 patients
IMRT compared with WBI	IBR	5 years	HR: 1.16; 95% CI: 0.23 to 5.80; I^2 =N/A	1 RCT,[9] 520 patients
	IBR	10 years	HR: 1.56; 95% CI: 0.55 to 4.40; I^2 = N/A	1 RCT,[9] 520 patients
	Overall survival	5 years	HR: 5.88; 95% CI: 0.71 to 48.51; I^2 =N/A	1 RCT,[9] 520 patients
	Overall survival	10 years	HR: 0.95: 95% CI: 0.50 to 1.80; I^2 =N/A	1 RCT,[9] 520 patients
IORT compared with WBI	IBR	5 years	HR: 9.30; 95% CI: 3.29 to 26.25; I^2 =N/A	1 RCT,[7] 1,305 patients
	IBR	>10 years	HR: 4.62; 95% CI: 2.68 to 7.96; I^2 =N/A	1 RCT,[7] 1,305 patients
	Overall survival	5 years	HR: 1.10; 95% CI: 0.67 to 1.81; I^2 =N/A	1 RCT,[7] 1,305 patients
	Overall survival	>10 years	HR: 1.07; 95% CI: 0.74 to 1.54; I^2 =N/A	2 RCTs,[7, 28] 4,756 patients

Abbreviations: 3DCRT = 3-dimensional conformal external beam radiation therapy; CI = confidence interval; HR = hazard ratio; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; N/A = not applicable; PBI = partial breast irradiation; RCT = randomized clinical trial; WBI = whole breast irradiation.

Table L.2. Meta-analysis by including Dodwell et al., 2005[6]*

Comparison	Outcome	Time	Findings	Study Design and Sample Size
PBI compared with WBI	IBR	10 years	RR: 1.33; 95% CI: 0.95 to 1.87; I^2= 0%	5 RCTs,[1-6, 9-13, 19, 22-24] 7,303 patients
	Overall survival	10 years	RR: 1.00; 95% CI: 0.98 to 1.03; I^2= 10.48%	5 RCTs,[1-6, 9-13, 19, 22-24] 7,303 patients
	Distant breast cancer recurrence	10 years	RR: 0.89; 95% CI: 0.51 to 1.54; I^2= 0%	4 RCTs,[1-6, 9-13, 22-24] 3,087 patients
Multi-modalities compared with WBI	IBR	10 years	RR: 1.32; 95% CI: 0.71 to 2.47; I^2 = 0%	3 RCTs,[1-6, 19] 4,648 patients
	Overall survival	10 years	RR: 1.02; 95% CI: 0.97 to 1.07; I^2 = 0%	3 RCTs,[1-6, 19] 4,648 patients
	Distant breast cancer recurrence	10 years	RR: 0.80; 95% CI: 0.05 to 13.93; I^2 = 0%	2 RCTs,[1, 6] 432 patients

Abbreviations: CI = confidence interval; IBR = ipsilateral breast recurrence; PBI = partial breast irradiation; RCT = randomized clinical trial; RR = relative risk; WBI = whole breast irradiation

* Dodwell et al, 2005[6] is a RCT conducted between 1986 and 1990 with antiquated radiation techniques that are no longer relevant to current practice but, otherwise, the study met our inclusion criteria.

Table L.3. Meta-analysis by the longest followup – KQ 1

Comparison	Outcome	Time	Findings	Study Design and Sample Size
PBI compared with WBI	IBR	Longest followup	RR: 1.27; 95% CI: 0.97 to 1.65; I^2= 0%	9 RCTs,[1-5, 9-27] 10,214 patients.
	Overall survival	Longest followup	RR: 1.00; 95% CI: 0.99 to 1.01; I^2= 0%	9 RCTs,[1-5, 9-27] 10,214 patients.
	Cancer-free survival	Longest followup	RR: 0.99; 95% CI: 0.97 to 1.01; I^2= 18.64%	6 RCTs,[1-5, 14-17, 19-26] 9382 patients.
	Cosmesis reported by healthcare provider (poor or fair)	Longest followup	RR: 0.76; 95% CI: 0.29 to 1.95; I^2= 90.22%	7 RCTs,[1-5, 9-18, 22-26, 38] 4,647 patients.
	Cosmesis reported by patient (poor or fair)	Longest followup	RR: 0.71; 95% CI: 0.05 to 10.26; I^2= 91.35%	4 RCTs,[9-17, 22-26] 4,085 patients.
3DCRT compared with WBI	IBR	Longest followup	RR: 1.15; 95% CI: 0.58 to 2.32; I^2= 0%	4 RCTs,[20-27] 3,720 patients.
	Overall survival	Longest followup	RR: 0.99; 95% CI: 0.97 to 1.02; I^2= 0%	4 RCTs,[20-27] 3,720 patients.
	Cancer-free survival	Longest followup	RR: 0.99; 95% CI: 0.95 to 1.04; I^2= 0%	3 RCTS,[20-26] 3,580 patients.
	Cosmesis reported by healthcare provider (poor or fair)	Longest followup	RR: 1.01; 95% CI: 0.03 to 31.77; I^2= 90.71%	3 RCTS,[22-26, 38] 2,369 patients.
	Cosmesis reported by patient (poor or fair)	Longest followup	RR: 2.31; 95% CI: 0.52 to 10.17; I^2= 0%	2 RCTs,[22-26] 2,237 patients.
IMRT compared with WBI	IBR	Longest followup	RR: 1.54; 95% CI: 0.01 to 467.42; I^2= 0%	2 RCTs,[9-13, 18] 692 patients.
	Overall survival	Longest followup	RR: 1.00; 95% CI: 0.88 to 1.14; I^2= 0%	2 RCTs,[9-13, 18] 692 patients.
	Cosmesis reported by healthcare provider (poor or fair)	Longest followup	RR: 0.33; 95% CI: 0.00 to ∞; I^2= 10.25%	2 RCTs,[9-13, 18] 692 patients.
	Cosmesis reported by patient (poor or fair)	Longest followup	RR: 0.05; 95% CI: 0.01 to 0.22; I^2= N/A	1 RCT,[9-13] 520 patients.
IORT compared with WBI	IBR	Longest followup	RR: 3.51; 95% CI: 0.19 to 64.59; I^2= 27.33%	2 RCTs,[7, 8, 28-37] 4,756 patients.
	Overall survival	Longest followup	RR: 1.01; 95% CI: 0.88 to 1.15; I^2= 0%	2 RCTs,[7, 8, 28-37]4,756 patients.

Comparison	Outcome	Time	Findings	Study Design and Sample Size
Multi-catheter interstitial brachytherapy compared with WBI	IBR	Longest followup	RR: 1.85; 95% CI: 0.62 to 5.49; I^2= N/A	1 RCT,[14-17] 1,328 patients.
	Overall survival	Longest followup	RR: 1.01; 95% CI: 0.98 to 1.03; I^2= N/A	1 RCT,[14-17] 1,328 patients.
	Cancer-free survival	Longest followup	RR: 1.00; 95% CI: 0.98 to 1.03; I^2= N/A	1 RCT,[14-17] 1,328 patients.
	Cosmesis reported by healthcare provider (poor or fair)	Longest followup	RR: 0.87; 95% CI: 0.58 to 1.32; I^2= N/A	1 RCT,[14-17] 1,328 patients.
	Cosmesis reported by patient (poor or fair)	Longest followup	RR: 1.08; 95% CI: 0.71 to 1.63; I^2= N/A	1 RCT,[14-17] 1,328 patients
Multi-modalities compared with WBI	IBR	Longest followup	RR: 1.26; 95% CI: 0.20 to 8.02; I^2= 0%	2 RCTs,[1-5, 19] 4,474 patients
	Overall survival	Longest followup	RR: 1.02; 95% CI: 0.89 to 1.17; I^2= 0%	2 RCTs,[1-5, 19] 4,474 patients
	Cancer-free survival	Longest followup	RR: 0.97; 95% CI: 0.80 to 1.17; I^2= 0%	2 RCTs,[1-5, 19] 4,474 patients.
	Cosmesis reported by healthcare provider (poor or fair)	Longest followup	RR: 0.56; 95% CI: 0.37 to 0.85; I^2= N/A	1 RCT,[1-5] 258 patients.

Abbreviations: ∞ = infinity; 3DCRT = 3-dimensional conformal external beam radiation therapy; CI = confidence interval; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable; PBI = partial breast irradiation; RCT = randomized clinical trial; RR = relative risk WBI = whole breast irradiation

Table L.4. Meta-analysis by longest followup – KQ 2

Comparison	Outcome	Time	Findings	Study Design and Sample Size
IMRT compared with 3DCRT	IBR	Longest followup	RR: 0.50; 95% CI: 0.00 to ∞ ; I^2= 50.09%	2 RCTs,[46, 47] 760 patients.
	Cancer-free survival	Longest followup	RR: 0.91; 95% CI: 0.87 to 0.95; I^2= N/A	1 RCT,[46] 656 patients.
	Cosmesis reported by healthcare provider (poor or fair)	Longest followup	RR: 0.05; 95% CI: 0.00 to 0.84; I^2= N/A	1 Observational study,[47] 104 patients.
	Cosmesis reported by patient (poor or fair)	Longest followup	RR: 0.06; 95% CI: 0.00 to 0.98; I^2= N/A	1 Observational study,[47] 104 patients.
Multi-catheter interstitial brachytherapy compared with 3DCRT	IBR	Longest followup	RR: 11; 95% CI: 0.25 to 483.88; I^2= N/A	1 Observational study,[51] 46 patients.
	Overall survival	Longest followup	RR: 0.72; 95% CI: 0.32 to 1.60; I^2= N/A	1 Observational study,[51] 46 patients
	Cosmesis reported by healthcare provider (poor or fair)	Longest followup	RR: 0.64; 95% CI: 0.32 to 1.27; I^2= N/A	1 RCT,[1-5] 125 patients.
Multi-modalities compared with IORT	IBR	Longest followup	RR: 0.28; 95% CI: 0.13 to 0.60; I^2= N/A	1 Observational study,[45] 617 patients
	Overall survival	Longest followup	RR: 1.00; 95% CI: 0.96 to 1.04; I^2= N/A	1 Observational study,[45] 617 patients
	Cancer-free survival	Longest followup	RR: 1.00; 95% CI: 0.99 to 1.02; I^2= N/A	1 Observational study,[45] 617 patients
Proton compared with 3DCRT	IBR	Longest followup	RR: 2.77; 95% CI: 0.50 to 15.44; I^2= N/A	1 Observational study,[41] 98 patients.
	Cosmesis reported by healthcare provider (poor or fair)	Longest followup	RR: 6.93; 95% CI: 1.81 to 26.49; I^2= N/A	1 Observational study,[41] 98 patients.
	Cosmesis reported by patient (poor or fair)	Longest followup	RR: 2.08; 95% CI: 0.20 to 21.75; I^2= N/A	1 Observational study,[41] 98 patients.
Single-catheter brachytherapy compared with 3DCRT	IBR	Longest followup	RR: 1.12; 95% CI: 0.00 to ∞; I^2= 0%	2 Observational studies,[51, 52] 377 patients.
	Overall survival	Longest followup	RR: 1.03; 95% CI: 0.94 to 1.14; I^2= N/A	1 Observational study,[51] 96 patients.
	Cosmesis reported by healthcare provider (poor or fair)	Longest followup	RR: 1.63; 95% CI: 0.72 to 3.72; I^2= N/A	1 Observational study,[52] 281 patients.
Single-catheter brachytherapy compared with multi-catheter interstitial brachytherapy	IBR	Longest followup	RR: 0.22; 95% CI: 0.01 to 4.62; I^2= N/A	1 Observational study,[51] 56 patients.
	Overall survival	Longest followup	RR: 1.44; 95% CI: 0.65 to 3.22; I^2= N/A	1 Observational study,[51] 56 patients.
	Cosmesis reported by healthcare provider (poor or fair)	Longest followup	RR: 0.67; 95% CI: 0.15 to 2.96; I^2= N/A	1 Observational study,[50] 103 patients.

Abbreviations: ∞ = infinity; 3DCRT = 3-dimensional conformal external beam radiation therapy; CI = confidence interval; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiotherapy; KQ = Key Question; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk

Appendix M. Additional Relevant Studies

Table M.1. Additional relevant studies*

Trial Acronym/Author Year, Trial Registration, Study Design	PBI Modalities	Conclusion (Effectiveness and Toxicity)
Cuttino, 2014,[53] single-arm observational study	APBI Contura	342 patients enrolled between January 2008 and February 2011 were followed at a median of 3 years. 10 patients (2.9%) reported IBR; 8 were true recurrences/marginal miss and 2 were elsewhere failures. 88% of the patients reported good or excellent cosmesis. Late toxicity. The incidence of infection was 8.5%. No patients reported grade 2-4 telangiectasia or fibrosis. Patients treated in high-volume centers reported better outcomes on cosmesis and toxicity.
Florence/Becherini, 2019,[54] NCT02104895, APBI arm from the Florence trial	APBI IMRT	22 patients with DCIS were followed at a median of 9.2 years. 17 patients were ASTRO suitable candidates while 5 patients were ASTRO cautionary. The overall survival was 90.9% at 10 years. One true IBR was recorded at 10.7 years. There was no contralateral invasive/DCIS occurrence, distant metastasis, or breast cancer–related death. Local recurrence, distant metastasis–free survival, and breast cancer–specific survival was 100% at 5 years and 10 years. Acute skin toxicity was observed in 3 cases (13.6%) (grade<2). No late toxicity was observed at 5 and 10 years. Patient reported cosmesis was excellent in 21 patients (95.5%) and good in 1 patient (4.5%).
Jagsi, 2010,[55] single-arm observational study	APBI IMRT (38.5 Gy in 3.85 Gy fractions twice daily)	With a median followup of 2.5 years, none of the 34 patients reported local failures. 7 patients (21.9%) had poor or fair cosmesis. The mean proportion of a whole-breast reference volume receiving 19.25 Gy (V50) and the mean percentage of the reference volume receiving 38.5 Gy (V100) was significant lower, when patients with good or excellent cosmesis were compared with those with poor or fair cosmesis.
Rehman, 2016,[56] single-arm observational study	APBI SAVI	132 patients were followed with a median of 1.7 years. 35 patients (26.5%) took pain medication during the treatment, while median and mode score for pain (measured from 0 no pain to 10 worst pain) was 0. 1 patient (0.8%) developed acute infection and 3 patients (2.3%) developed late infection. Other late toxicities included grade 1 or 2 hyperpigmentation (43.9%), telangiectasia (0.8%), grade 1 seroma (9.1%), grade 1 or 2 fat necrosis (5.3%), and grade 1 or 2 fibrosis (12.1%). Local recurrence rate was 3.8% at a median of 1.9 years after radiation therapy. 5 patients developed a local recurrence at a median of 1.92 years. Of them, 2 patients were ASTRO suitable candidates, 1 patient was cautionary, and 2 patients were unsuitable.
RTOG 95-17,[57] single-arm observational study	APBI multi-catheter interstitial brachytherapy	98 patients were followed at a median of 11.3 years. 15 patients (15%) reported fat necrosis (grade 2: 10 patients; grade 3-4: 5 patients). Grade 1–2 skin toxicity was reported in 78% of the patients and grade 3 in 13%. No patients reported grade 4 toxicity. At 5 years, 66% of the patients and 68% of the radiation oncologists reported good or excellent cosmesis.
TRIUMPH-T,[58] NCT02526498, single-arm observational study	APBI single-entry catheter brachytherapy (SAVI, Contura), or multi-catheter interstitial brachytherapy	200 patients were followed at a median of 1 year. 77 patients (38.5%) reported 116 adverse events. 96% of these adverse events were grade 1 to 2. 97.25% patients reported good/excellent cosmesis. 1 patient (0.5%) reported in-breast tumor recurrence (with bone metastasis) and 1 patient (0.5%) reported regional nodal failure. No other recurrence was reported.

Trial Acronym/Author Year, Trial Registration, Study Design	PBI Modalities	Conclusion (Effectiveness and Toxicity)
Jethwa, 2018,[59] single-arm observational study	APBI single-entry catheter brachytherapy	73 patients were followed at a median of 14 months. No patients died or reported relapse. At 1 year, 95% patients reported good or excellent cosmesis and 91% reported overall quality of life as ≥8 of 10. 2 patients (3%) reported breast infections. No other grade ≥2 treatment-related adverse events were observed.
Vicini, 2011,[60] single-arm observational study	APBI MammoSite	Of the 1,440 patients (1449 breasts), IBR was reported in 37 cases (2.6%) with a 5-year actuarial rate of 3.8% (3.9% for IBC and 3.4% for DCIS). 93.3% cases reported good or excellent cosmesis at 3 years, 90.5% at 4 years, 90.6% at 5 years, and 85.3% at 6 years. 28.0% patients reported seromas, 35.5% with open cavity placement, 21.7% with closed cavity placements. 33 cases (2.3%) developed fat necrosis.
Yashar, 2011,[61] single-arm observational study	APBI SAVI	At a median of 1.8 years, 1 of the 102 patients (0.98%) reported in-field recurrence. 2 patients (1.9%) developed telangiectasia; 10 (9.8%) grade 1 hyperpigmentation; 2 (1.9%) grade 2 fibrosis; 2 symptomatic Seromas (1.9%); and 2 cases of asymptomatic fat necrosis (1.9%).

Abbreviations: APBI = accelerated partial breast irradiation; ASTRO = American Society for Radiation Oncology; DCIS = ductal carcinoma in situ; Gy = gray; IBC = invasive breast cancer; IBR = ipsilateral breast recurrence; IMRT = intensity-modulated radiotherapy; PBI = partial breast irradiation; SAVI = Strut-Adjusted Volume Implant; V = volume of a structure receiving a given dose of radiotherapy expressed as either a percentage of the prescription dose (e.g. V100%) or as a quantity of dose (e.g. V30Gy)

*These studies do not meet the eligibility criteria for this systematic review. However, they may provide additional information.

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